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Research Article

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

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Abstract

Polymeric coating techniques have been widely used in the pharmaceutical industries for diversified reasons. 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 coating material for developing coated pellets for sustained release of drug and comparing it with well known ethyl cellulose as hydrophobic polymeric material. Drug layered NPS, drug loaded pellets prepared with extrusion spheronization and NPS coated with drug polymer matrix were used as multi particulate formulation. The results indicate that Gum Sandarac is very efficient in retarding release of drugs from different pellet formulations yielding very superior quality pellet.

Keywords: Pellets, Sandarac, polymer coating, Diclofenac sodium, Propranolol Hydrochloride, ethyl cellulose

1.Introduction

Polymeric coating techniques have been widely used in the pharmaceutical industries to mask undesirable taste, odour and colour of formulation, facilitate the swallow-ability of dosage forms, protect drug from air, moisture or light and improve the appearance of the product [1], but mostly for the controlled/sustained release of drugs [2-4]. The conventional process of polymeric coatings involves the drug loading onto tablets, granules, pellets or sugar spheres, and the subsequent application of a thin polymeric film onto the surface of a solid substrate with polymeric solutions using coating apparatuses [5, 6]. Drug loading and polymeric coating for controlled release can be achieved using a separate process as the drug is not included in coating dispersions. Drug loading can be achieved either by formulating tablets or pellets of drug with inert excipients or coating drug on plain excipients containing core tablets or pellets. A typical coating is approximately 25–100 μm in thickness. Various pharmaceutical excipient and other related substances, such as plasticizers, solubilizers, surfactants, oils, fatty acids and talc, can also be added into the polymeric coating solution to modify the physical properties of the dried films [7-10]. The release rate from dosage form can also be modified by applying drug containing polymeric coating dispersions onto cores. In this system, simultaneous drug–loading and controlled release can be achieved after casting drug: polymer solution into coated films [11, 12]. Various surfactants and solubilizers may also be incorporated into the drug–containing polymeric dispersions for poorly water–soluble drugs [3, 11], for effective controlled release dosage from for poorly water–soluble drugs to assist the solubility and dissolution rate. The mechanisms involved in the control of drug release from coated dosage forms are complex and not yet fully understood [13-17]. Upon contact with aqueous human body fluids, water diffuses into the coated systems (due to concentration gradients) and dissolves the drug. The dissolved drug subsequently diffuses out of the dosage forms through the coatings which controls the overall drug release rate. In addition, due to the imbibing water, significant hydrostatic pressures can be created within the cores. These hydrostatic pressures can lead to the formation of cracks within the polymeric films and, thus, to significant changes in drug permeability.

Numerous film forming materials have been investigated for drug delivery applications. These include Cellulose acetate phthalate [18], HPMC, Ethyl Cellulose [19], Hydroxy Ethyl Cellulose, Methyl Ccellulose and Hydroxy Propyl Cellulose [20-23]. Also, polyvinyl alcohol, [24], polyvinyl chloride [25], chitosan derivatives [26], starch derivatives [27,28], shellac [29-31] and methacrylic acid copolymers [32-34] have been widely used to coat the solid dosage forms. However, a range of these has certain advantages as well as own limitations [35]. Although, this scratches the surface of information of some of the various polymeric materials that are investigated as coating agents, it projects the need to explore the novel polymeric materials for sustained drug delivery. It is therefore prerequisite to investigate the novel film forming materials to coat the solid dosage forms. Sandrac gum is a resin obtained by incision from the stem of *Callitris quadrivalvis*, Ventenat (N.O. Coniferae) Pinaceae. It has been used as additive in medicines for various purposes and is a very safe gum resin for internal use [36-38]. Though extensive chemical analysis and research have been carried out with Sandarac [39-41], till date it has not been used as sustained release agent. Taking into consideration the prospective of coating processes, 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 coating material for developing coated pellets for sustained release of drug and comparing it with well known ethyl cellulose as hydrophobic polymeric material.

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2. Materials

Diclofenac sodium (DFS) was received as gift sample for research 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 was procured from Loba Chemicals Mumbai.. All other ingredients were of AR grade and purchased from SD Fine Chemicals India. Materials were used as received.

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°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 plain pellets of drugs

Either PRP or DFS (10%), MCC (58%), lactose (20%) and PVP K–30 (2%) were used to prepare the plain pellets by extrusion spheronization. The drug and diluents were blended in polybags. The blend was wetted with the solution of the PVP in small amount of water. The desired wetting end point was achieved by adding additional distilled water. The wet cohesive mass was extruded through the extruder (Umang Pharmatech, Mumbai) with a die roller of 1.5 mm diameter at 35 rpm. The obtained extrudates were spheronized for 7 min on a spheronizer (Umang Pharmatech, Mumbai) using cross–hatch friction plate with topless prism shaped grooves (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 polymer coating.

3.3. Polymer coating

Conventional spray coating technique was used for developing coated pellet formulations. Drug containing pellets in coating pan were coated by spraying 15% w/v solutions of GS in acetone isopropyl alcohol and 5% w/v solution of EC in alcohol on cascading pellets with spray gun. The spray rate of the coating solution was maintained at 1–2 ml/min, with the spray gun positioned at 10–15 cm from pellet bed surface. Atomizing air pressure of 15–25 psi was used for coating. The rotational speed of coating pan was set to 35 rpm throughout the study. The temperature of the pellet bed was kept 45–50˚C using a hot air blower. Sufficient coating material to achieve 10 % weight gain was applied to the drug layered pellets. Talc (0.4% w/w) was sprinkled intermittently to avoid sticking of pellets during the coating protocols. The formulation batches for pellets coated with polymers are shown in Table No. 1.

Table No. 1: Formulations Of Drug Containing Coated Pellets

Ingredients % w/w	Formulations			
	F1	**F2**	**F3**	**F4**
PRP	10	–	10	–
DFS	–	10	–	10
EC	10	10	–	–
GS	–	–	10	10
PEG 400*	10	10	10	10

* PEG 400 concentration was calculated with respect to polymer w/w

3.4. Preparation of Drug–layered and polymer coated pellets

Non–peril seeds (NPS) of 16/20–mesh size were taken into coating pan and DFS solution, 20% w/v in alcohol and PRP solution in water alcohol mixture (1:5 v/v) containing povidone (1% w/v) was sprayed intermittently over the cascading NPS using a spray gun to achieve a 10% w/w drug layering on NPS. Hot air was blown occasionally to evaporate the solvent.

The pellets were coated with polymers in similar fashion as mentioned in above section.

Table No. 2: Formulations Of Drug Layered Coated Pellets

Ingredients % w/w	Formulations			
	F5	**F6**	**F7**	**F8**
PRP	10	–	10	–
DFS	–	10	–	10
EC	10	10	–	–
GS	–	–	10	10
PEG 400*	10	10	10	10

* PEG 400 concentration was calculated with respect to polymer w/w

3.5 Preparation of drug polymer matrix coated pellets

Drug and polymer in 1:2 ratio were dissolved in respective solvent alcohol for EC and acetone alcohol (1:1) for GS. The drug polymer solution was coated on NPS as mentioned in above sections.

Table No. 3: Formulations of Drug Polymer Matrix Coated Pellets

Ingredients % w/w	Formulations			
	F9	**F10**	**F11**	**F12**
PRP	10	–	10	–
DFS	–	10	–	10
EC	20	20	–	–
GS	–	–	20	20

3.6. Evaluation of pellets

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.

3.6.1. 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 spectrophotometrically (UV–1601, Schimadzu, Japan) at 276nm and 289 nm for DFS and PRP contents respectively.

3.6.2. Drug release studies

The drug release study was carried out in USP XXIV dissolution apparatus I (Basket; Veego Scientific, India) at 75 rpm and 37 ±0.5°C. Phosphate buffer pH 6.8, 900 ml, was used as dissolution medium. Hourly 10 ml of the sample was withdrawn and replaced with the equal volume of fresh medium. The withdrawn samples were filtered 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.

3.7. Stability studies

The pellet formulations were kept at 30°C and 40°C for stability testing and examined for physical appearance, crushing strength, drug content and in vitro dissolution after 30, 60 and 90 days. An attempt was made to conduct the stability study as per International Conference on Harmonization of technical requirements for the registration of pharmaceuticals for human use (ICH) guidelines using specific combinations of temperature and relative humidity (RH), however, it was not endurable simultaneously to maintain both the temperature and RH in the existing laboratory facilities. Therefore, the study was conducted at above specified temperature and laboratory–RH (40–50%).

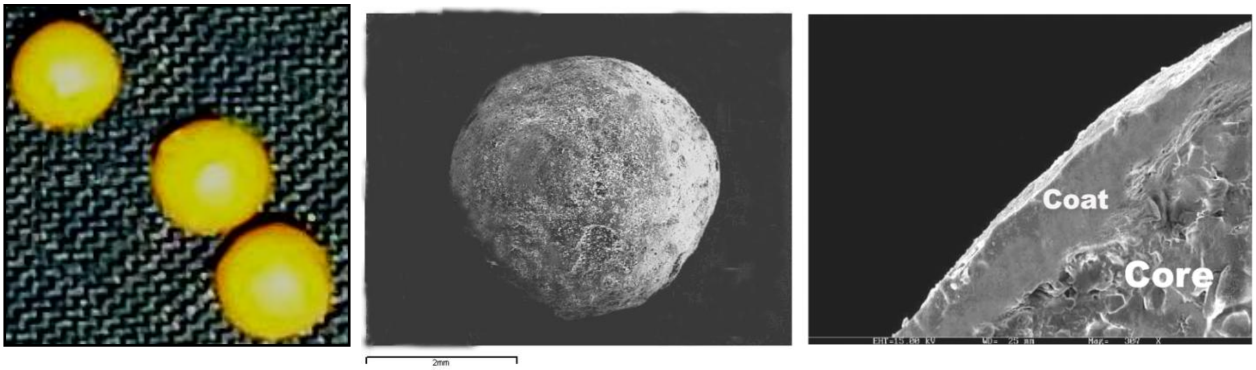
4. Results and discussion

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 pikes of drug substance indicating no incompatibility.

4.2. Evaluation of pellets

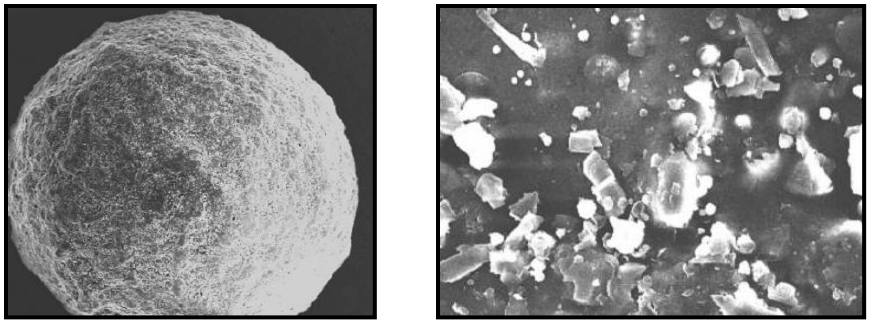
The pellets utilized for evaluating coated dosage form were of # 14/16 size range and uniform in size and hence coated pellets were not analyzed for the size distribution as that for matrix pellets. The drug loaded and plain pellets for drug layering, formed by extrusion spheronization, were spherical and smooth to visual observation. The sphericity index of all the pellets after polymer coating was above 0.6 indicating good sphericity. The microphotograph and SEM of GS coated DFS pellets are shown in **Fig 1.**



(A) **(B)** **(C)**

Fig. 1.:Microphotograph and SEM of GS coated pellets (A) GS coated DFS pellets (B) SEM of GS coated DFS pellet 30X (C) SEM cut view of coated pellet 1000X

Matrix coated pellets were very good surface texture and smoothness and as only NPS were used very uniform and spherical. The drug particles are embedded in coated polymer film and hence the polymer coat is in the form of drug polymer matrix and hence this coating technique is referred as matrix coating. The SEM of GS: DFS matrix coated pellets are shown in **Fig. 2.**



30X **500 X**

Fig. 2: SEM of GS: DFS matrix coated pellet

4.1.1. Crushing strength and friability of the pellets

The crushing strength and friability values of pellets are summarized in Table No. 4. The EC and GS coated pellets showed crushing strength in the range of 1.3–1.5 kg/cm^2. The drug polymer matrix coated pellets showed crushing strength in the range of 1.4–1.6 kg/cm^2.The EC and GS coated pellets showed very low friability and good drug content.

4.1.2. Hausner ratio and compressibility index

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 of excellent flowability. All the pellets formulations show excellent flow properties. Hausner ratio of all formulation batches also indicates good flow properties.

Table No.4: Physical Properties Of Coated Pellets

Formulations	Parameters studied					
	Shape factor	Crushing strength (Kg/cm^2)	(%) Friability	Hausner ratio	Comresibility index	Drug content
F1	0. 85	1. 4	0. 32	1.08	8. 19	99.21
F2	0. 83	1. 4	0. 24	1.07	7. 09	98.92
F3	0. 82	1. 3	0. 34	1.08	8. 21	99.12
F4	0. 84	1. 5	0. 37	1.06	6. 22	99.89
F5	0.73	1. 4	0. 40	1.07	7. 12	98.90
F6	0.75	1. 4	0. 38	1.07	6. 98	99.02
F7	0.78	1. 3	0. 44	1.08	8. 12	99.14
F8	0.77	1. 5	0. 43	1.07	7. 24	99.34
F9	0.88	1. 5	0. 34	1.08	8.23	99.75
F10	0.83	1. 4	0. 37	1.09	9.29	99.81
F11	0.79	1. 6	0. 38	1.08	8. 09	99.73
F12	0.82	1. 5	0. 34	1.09	9. 32	99.23

4.2. Drug release study

4.2.1. Polymer coating on drug containing loaded pellets

During lab trials tablets with 5% coating and 7% coating were also prepared and evaluated. but there was no much retarding effect in case of 5% due to insufficient coating and 7% coat gave faster release after initial very slow release hence data of only 10% is shown in results. The solubility behaviour of both the polymers GS and EC is similar and drug DFS shows pH dependent solubility with solubility increasing at higher or basic pH values with no solubility at acidic pH of the range 1.2, hence dissolution was carried out in 6.8 phosphate buffer directly after initial trials. During Initial lab trials, for first two hours, dissolution was carried out in 1.2 pH HCl solution buffer but there was very low drug release and the pellets were seem to be not affected much by exposure to acidic pH. To maintain uniformity all the formulations were tested directly at 6.8 pH phosphate buffer.

The preliminary lab trials showed that plain GS and EC coat was practically impermeable and gave insufficient drug release in 8 hours. Therefore PEG 400, 10%w/w with total polymer weight in coating solution, was selected and incorporated in the polymer coating as channelling agent as well as plasticizer. The drug release profiles of GS and EC 10 % coated DFS pellets, containing 10% PEG 400, in 6.8 phosphate buffer are shown in **Fig. 3**. The coating level of 10 % was very effective in sustaining DFS release for more than 8 h in phosphate buffer pH 6.8 giving only 71.03 % for GS and 68.21 for EC coating. Although the drug release–retarding ability primarily should be attributed as the characteristic of polymeric material, effect of drug itself on its release profile cannot be ignored.

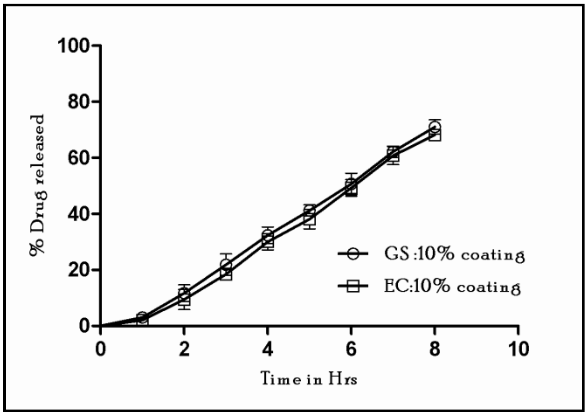


Fig. 3: DFS release profile from EC and GS coated drug loaded pellets

The drug release profile of GS and EC 10 % coated PRP pellets is shown in **Fig. 4**. A 10 % w/w coating level of GS could sustain the PRP release for more than 8 h giving about 88.67 % release while EC showed 92.21 % release.

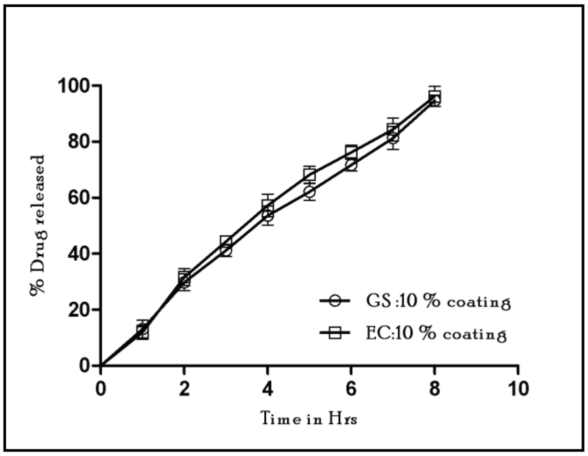
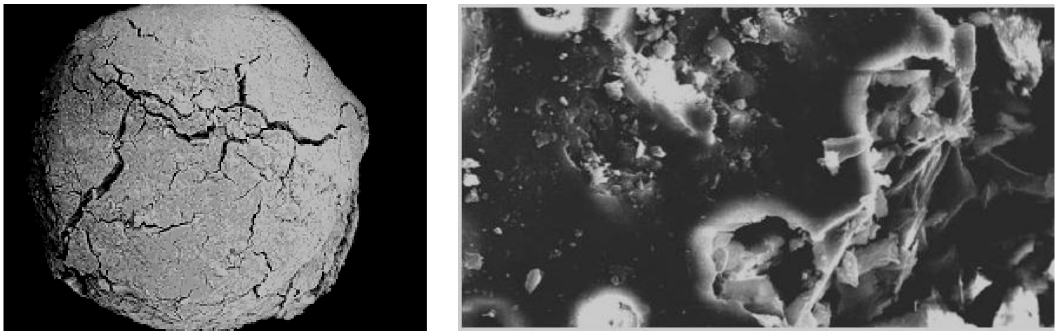


Fig. 4: PRP release profile from EC and GS coated loaded pellets

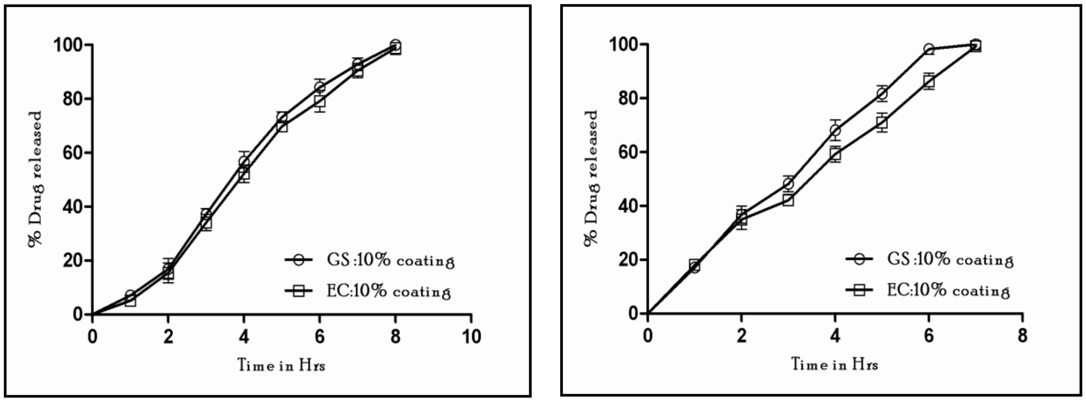
As per anticipation, DFS pellets showed slow drug release compared to PRP. This may be due to the low solubility of DFS as compared to PRP. SEM of pellets after dissolution is shown in Fig.5



30X 500X

Fig. 5: SEM GS coated DFS pellets after dissolution

4.2.2. Polymer coating on drug layered pellets In the case of drug layered pellets the entire drug was present on the pellets periphery in contrast to drug loaded or drug containing pellets where the drug is embedded in so called matrix of diluent or spheronization aid MCC. The drug has to diffuse from polymer layer only to get released from the coated pellets while in case of drug loaded pellets the drug has to first cross pellet core made up of diluent (MCC in this case) and then diffuse through polymer coat. The drug release profiles of EC and GS coated drug layered pellets of DFS and PRP are shown in **Fig. 6.**



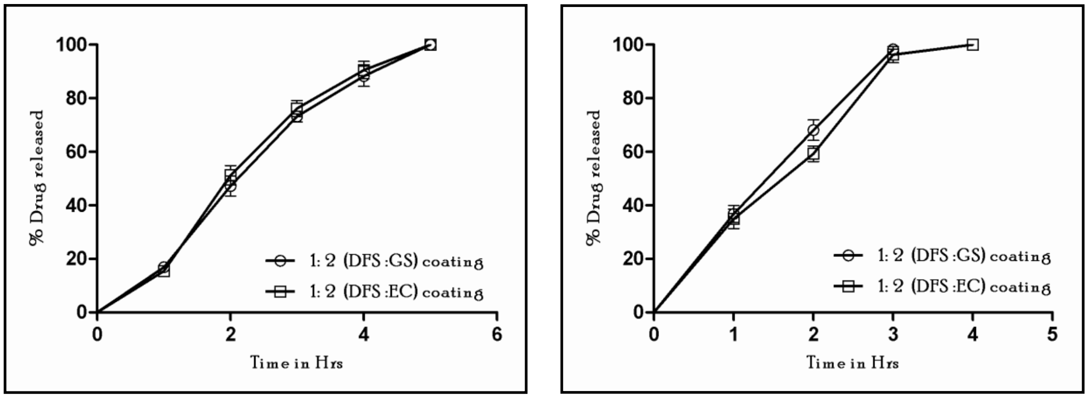
(A) **(B)**

Fig. 6.: Drug release profile from EC and GS coated drug layered pellets (A) DFS release (B) PRP release

DFS was released completely in 8 hours with both the polymers while PRP was released completely in 7 hours and PRP release was quite linear as compared to DFS.. The initial release of DFS was very slow and was somewhat linear for 4 hours but once all the drug was solublised and channels were formed the drug released quite rapidly. Initial PRP release was faster as compared to DFS release. Higher solubility can be reasoned for this. The breakdown of polymer films coat due to higher osmotic pressure caused by solublization of peripheral drug might have resulted in slightly higher amount of pores in coat and higher release.

4.2.3. Drug polymer matrix coating

In matrix coating drug dissolved or dispersed in polymer solution is coated on inert core like NPS. Matrix coating system is very convenient form of coating as it is a one step process and economic with time and cost. The drug particles are embedded in coated polymer film and hence the polymer coat is in the form of drug polymer matrix and hence this coating technique is referred as matrix coating. The drug release profile of matrix coated pellets of DFS and PRP with GS an EC at 1:2 ratio are shown in **Fig 7.** The different ratios like 1:3 and 1:4 are not reported.



(A) (B)

Fig. 7: Drug release profile from drug: polymer matrix coated pellets (A) DFS release (B) PRP release

The initial release of DFS pellets was improved markedly with matrix coating. DFS was released completely in 5 hours with both GS and EC. PRP pellets gave very fast initial release showing complete drug release in 3 Hrs for GS and in 4 Hrs for EC. The initial fast release can be attributed to the solubilisation of surface drug in the surrounding media. SEM of pellets coated with drug polymer matrix is shown in Fig. 8.

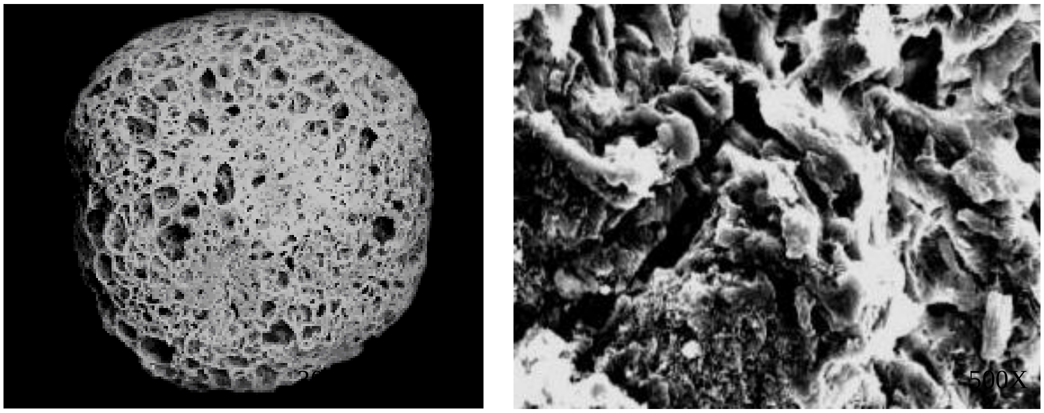
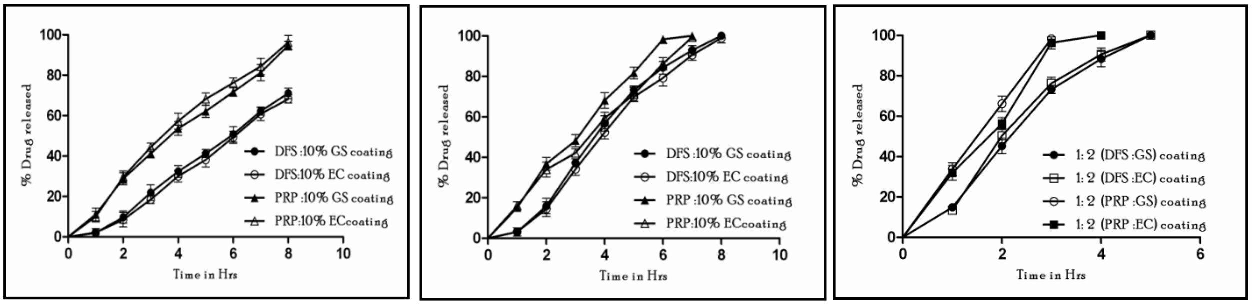


Fig. 8: SEM of GS: DFS matrix coated pellets after dissolution

4.4. Stability study

All the pellets exhibit good stability over the period of stability test. The physical evaluation of pellets showed no change at all in all evaluatory parameters. No significant change in the drug release profile of coated pellets was observed when these were kept at 30°C for 90 days ($p > 0.05$). A slight decrease in the initial drug release rate of coated pellets was observed when these were kept at 40°C for 90 days (**Fig. 9**). Uncoated pellets showed no noteworthy change in release profile when kept at 40°C for 90 days.



EC GS Loaded **EC GS Layered** **Matrix coated**

Fig. 9: Drug release profile from coated pellets after stability testing period of 90 days

4.5. Conclusion

Gum sandarac is very efficient coating material with ideal properties for coating showing comparable coating qualities and sustained action with ethyl cellulose. Drug release from the drug loaded pellets can be sustained for prolonged period as compared to drug layered pellets. Matrix coating can be a efficient, economic and time saving coating system and need to be evaluated in depth to yield desirable coating properties. Thus it can be concluded that gum sandarac ha good potential as release retarding coating material.

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