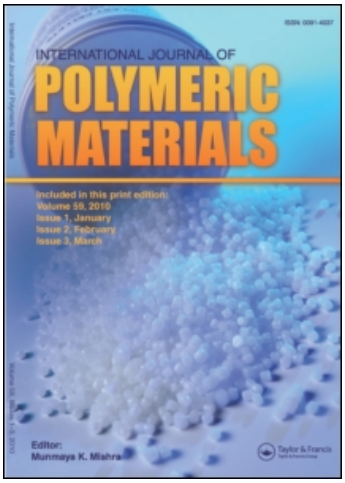

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2-HEMA-g-Na-PCMS: A Novel Polymeric Matrix for the Controlled Release of Paracetamol

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2-hydoxyethyl methacrylate (2-HEMA) was graft copolymerized with sodium salt of partially carboxymethylated starch (Na-PCMS). Thus prepared, graft copolymer (2-HEMA-g-Na-PCMS) was used as a polymeric matrix for preparing controlled-release tablets of paracetamol. Tablets of standard specification were prepared using the wet granulation method. Ingredients utilized for tablet preparation were 2-HEMA-g-Na-PCMS graft copolymer, paracetamol and excipients. Tablets were characterized for disintegration time (min), hardness, angle of repose and percent friability. It was found that tablets prepared by the compression of graft copolymer, excipients and drug in specified ratios resulted in an excellent controlled-release tendency of paracetamol.

Keywords: graft copolymer, in vitro evaluation, paracetamol, wet granulation tablet properties

INTRODUCTION

During the past one-and-a-half decades, the pharmaceutical industry has invested vast amounts of time and money in the study of tablet compaction. This expenditure is quite reasonable when one considers how valuable tablets, as a dosage form, are to the industry. As oral

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dosage forms can be self administered by the patient, they are obviously more profitable to manufacture than parenteral dosage forms, which usually must be administered by trained personnel. This is reflected by the fact that well over 80% of the drugs in the United States that are formulated to produce systemic effects are marketed as oral dosage forms. Compared with other oral dosage forms, tablets are the manufacturer dosage forms of choice because of their relatively low cost of manufacturing, packaging and shipping, increased stability and virtual tamper resistance, i.e., most tampered tablets either become discolored or disintegrate [1]. In 1966, a system was developed by Huber et al. [2], describing a novel approach for controlling the release rate of drug substance from tablet formulation. The method described involves mixing a medicament/medicinal agent or agents with certain nondigestible, hydrophilic gum and compressing the mixture into tablets. A matrix is defined as a well-mixed composite of ingredients fixed into a shape by tableting or use of a hard shell capsule. There have been many products utilized to elaborate controlled-release systems, depending on the drug that is going to be used and the effect it is designed for Cellulose and starch derivatives have long been used for their ability to sustain the release of drugs [3]. Synthetic polymers, such as methacrylate, have attracted wide attention in the controlled release of drugs due to their nontoxicity along with their ease of polymerization at lower cost [4–6]. On the basis of this knowledge, we have tried to utilize our past experience in the synthesis of graft copolymers in the aim of obtaining a product potentially suitable to be used as a sustained or controlled-release matrix here, we chose the sodium salt of partially carboxymethylated starch with poly(hydroxyethyl methylacrylate), that is a highly biocompatible polymer widely used in the pharmaceutical industry [5–8].

In light of the above, we have synthesized and characterized first sodium salt of partially carboxymethylated starch (Na-PCMS), and then novel graft copolymer 2-HEMA-g-Na-PCMS using CAN as an initiator [9–10]. Then, focused on ascertaining the tablet formulation techniques, the suitability of the novel graft copolymer 2-HEMA-g-Na-PCMS for controlled action of paracetamol, the mechanical properties of tablets and release pattern were characterized.

MATERIALS AND METHODS

Paracetamol IP was received from Borsad, Gujarat, India. Starch, lactose, Mg-stearate, and talc were procured from SD Fine Chemicals, Mumbai. Graft copolymers were used after purification. All other

chemicals and reagents used were of L.R. grade and were used as procured.

Preparation of Sodium Salt of Partially Carboxymethylated Starch (Na-PCMS)

Na-PCMS was synthesized by standard slurry method as reported by N. K. Patel et al. [9].

Starch and isopropanol were stirred vigorously, while the required amount of 30% (w/v) aqueous NaOH was added dropwise during 10 min at room temperature. Stirring was continued for 1 h to activate the starch. Then, sodium monochloroacetate was added. The mixture was placed on a water bath at 55°C for 5 h with stirring. Then the product was filtered, suspended in methanol and neutralized with acetic acid, then washed with ethanol and dried at 60°C.

Preparation of 2-HEMA-g-Na-PCMS

2-HEMA-g-Na-PCMS was prepared as reported by N. K. Patel et al. [10].

In a typical graft copolymerization reaction, Na-PCMS was stirred in double-distilled water and purged with a slow stream of nitrogen for 1 h at 25–30°C. A freshly prepared solution of 0.3 M cerric ammonium nitrate (CAN) in 0.3 M HNO_3 was added and stirred for 20 min. Then, distilled 2-HEMA monomer was added. Grafting reaction was carried out for 4 to 4.5 h. The crude copolymer was filtered and washed with HNO_3 and distilled water. The homopolymer (PHEMA) formed during the process was removed by extraction with dimethylformamide (DMF) and the pure product dried under vacuum at 50°C until constant weight was obtained.

Preparation of Matrix Tablets

Tablets were prepared by the wet granulation method. Five different batches, B1, B2, B3, B4 and B5 were prepared by keeping paracetamol (12 g) and lactose (8 g) constant, and changing the amount of graft copolymers HEMA-g-Na-PCMS (binder) in the amounts of 120, 240, 360, 480 and 600 mg, respectively. The mass was mixed in a mortar with a small amount of doubly distilled water. The pasty mass was passed through a #10 s.s. mesh. It was then dried at 50°C in a vacuum dryer. After complete drying, the mass was again sieved through #22 mesh. The oversize was called granules and the undersize as fines. Granules and fines were kept separately. The granules were mixed

with 2% fines, 1 % magnesium stearate, 1% talc and 5% starch, before being molded into individual tablets.

Flow Property of Powder

The static angle of repose was measured according to the fixed funnel and free standing cone method [11]. A funnel with the end of the stem cut perpendicular to its axis of symmetry is secured with its tip 2 cm above a graph paper placed on a flat horizontal surface. Powder is carefully poured through the funnel until the apex of the cone thus formed just reaches the tip of the funnel. The mean diameter of the base of the powder cone is measured and the tangent of the angle of repose is obtained. The following standard physical tests were performed on the tablets prepared.

Weight

The weight (mg) of each of the 40 individual tablets was determined by dusting each tablet off and placing it on an electronic balance.

Thickness

The individual thickness of tablets was determined by placing it parallel to the jaw of a micrometer.

Friability

It was determined by weighing fifteen tablets after dusting, placing them in a friability tester and rotating the basket vertically at 25 rpm for 4 min (100 drops). Afterwards the total remaining weight of the tablets was recorded and the percent friability was calculated.

$$\%\,\text{Friability} = \frac{\text{Original Weight} - \text{Final Weight}}{\text{Original Weight}} \times 100$$

Disintegration testing was performed at 37°C in double-distilled water using Tablet Disintegration Test Machine, I. P. third edition, Sentwin India, Ltd.

Hardness

It was performed with the help of a manual hardness tester.

In Vitro Dissolution Studies

The dissolution test was carried out for tablets using 900 ml phosphate buffer pH 7.8 as the medium and rotating the paddle at 50 rpm for 30 min. A suitable volume of the sample was withdrawn and filtered. The first few ml of filtrate were rejected and the remaining were diluted with the same solvent. Absorbance of the resulting solution at the maximum at about 249 nm was measured. Similarly, absorbance of a solution of known concentration of paracetamol reference standard was measured. The content of $C_8H_9NO_2$ relative to the declared content of $C_8H_9NO_2$ in paracetamol reference standard was determined.

RESULTS AND DISCUSSION

The choice of the polymeric excipients is of obvious importance to get the desired release profile. Table 1 gives the result of the tablets prepared by direct pressing. They pass the test for weight uniformity. That suggests a good flowability of the powder. The friability values for the tablet batches B4 and B5 are acceptable, which should be below 2% [12]. The low friability values obtained here can be explained by the fact that the moderate binding properties of this material results in lower friability values. The disintegration time is in decreasing order with respect to the increasing amount of binder, confirming the moderate binding properties.

It is necessary for the powder prepared to have good flow properties for tablet manufacturing. Also the powder must have the correct value of the angle of repose. Here, according to the results, the values obtained for the angle of repose suggests that the mixture showed good flow property [13]. The values of hardness are shown in Table 1. From this we may say that the hardness of the tablet increases with the amount of binder used. Table 2 depicts the profiles of the in vitro dissolution test for the different batches of tablets under study. We can

TABLE 1 Properties of Paracetamol Tablets Prepared

Sr. No.	Angle of repose (degree)	Disintegration (minutes)	Friability (percent)	Hardness (kg)	Weight variation (mg)
B1	37.29	19.15	2.51	5.3	520.4
B2	37.64	18.33	2.60	5.7	525
B3	36.43	17.15	2.30	5.9	509.1
B4	37.30	16.20	1.30	6.0	507.5
B5	40.29	15.45	1.30	6.5	499.3

TABLE 2 Release of Paracetamol from Standard Tablet and Various Batches

	% drug release					
Time (minute)	B1	B2	B3	B4	B5	Standard paracetamol tablet
15	8	5	4	3	3	15
30	14	9	6	5	4	20
45	18	12	9	7	6	24
60	23	26	13	9	7	28
75	26	20	17	12	10	33
90	30	24	21	15	13	37
105	33	29	25	20	18	40
120	38	32	30	24	20	45
135	42	34	33	28	25	48
150	46	38	38	31	28	53
165	50	42	42	35	31	58
180	52	47	45	38	33	62
195	54	52	48	40	35	65
205	55	54	52	40	38	68
220	56	55	52	40	38	73
235	56	55	52	40	38	75
250	65	55	52	40	38	80
265	65	55	52	40	38	83
280	65	55	52	40	38	87
295	65	55	52	40	38	92
305	65	55	52	40	38	94
320	65	55	52	40	38	100

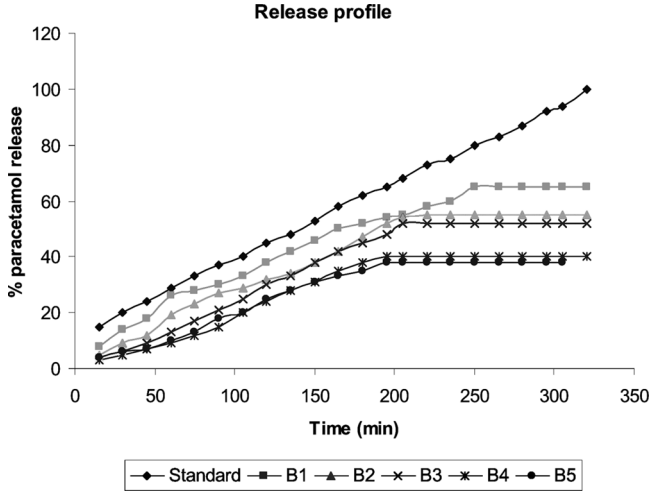

FIGURE 1 Release profile of paracetamol at 37°C in phosphate buffer (pH = 7.4).

clearly observe the decrease release of the drug amount as compared to the reference standard in all the batches prepared as shown in Figure 1. A possible explanation of these results can be found in the effect of the particle size of the polymers. It was reported that tablets prepared from finer particles of polymer exhibited slow release [14]. All the values of % release are lower than of the standard paracetamol tablets.

CONCLUSION

In conclusion, we may assess that good quality tablets may be prepared from the ingredients suggested in formulation, and good results are obtained from controlled-release matrix tablets prepared with graft copolymer 2-HEMA-g-Na-PCMS. So, this polymer finds suitability as a controlled-release agent or we may say that release of drug may be controlled with the aid of graft - copolymer. The tablets prepared using the above formulation have good physical properties. Finally, the percentage of drug release is lower than with the ordinary paracetamol tablet with the same drug content. The results are encouraging and findings are fruitful.

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