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PREPARATION AND EVALUATION OF SUSTAINED RELEASE INDOMETHACIN NONPAREIL SEEDS

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ABSTRACT

A controlled release oral drug delivery system of Indomethacin was developed using nonpareil seeds as a matrix system. These seeds were coated with different concentrations of drug release controlling materials viz Eudragit RL100 and Eudragit RS100, and bees wax. The particle size of the seeds and the concentration as well as the type of the drug release controlling Eudragits has a pronounced effect on the release rate profile of Indomethacin. All types of formulations showed release rate pattern which can be described by both first-order and diffusion controlled mechanism.

INTRODUCTION

Nonpareil seeds, as a method for the preparation of controlled release oral dosage forms, is of considerable interest. Generally, nonpareil seeds are

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spherical bodies formed from a mass of finely divided particles by a continuous rolling or tumbling motion (1). Several approaches were utilized for the preparation of spherical particles for subsequent coating with drug release-controlling materials (2-5). The traditional method of building up cores, which include crystals, nonpareil seeds and granules for spheronization is by the use of conventional coating pan(5). The effects of raw materials and processing conditions on the quality of the finished product for this layering process were studied (6,7).

Indomethacin is an effective non-steroidal anti-inflammatory agent and a potent prostaglandin inhibitor. Its bioavailability is related to a very low aqueous solubility (0.01 mg/ml) and hence the absorption of the drug is controlled by its rate of dissolution in the G.I. fluid (8). Controlling the release of Indomethacin is an important therapeutic aspect, because instantaneous release of the drug from the dosage form produces serious gastrointestinal, irritation as well as dose dumping effect (9). In addition, the controlled release dosage form of Indomethacin would be capable to maintain steady plasma level of the drug and reduce the frequency of administration (10).

Methacrylate ester copolymers viz Eudragit RL100 or Eudragit RS100 are neutral polymers and are insoluble in the entire physiological pH-range. However, they possess a defined swelling capacity and permeability with respect to water and dissolved drugs, which are independent of pH. These polymers are inert and particularly suitable for the manufacture of retarded drug formulations (11-15).

The objective of this study was to obtain controlled release Indomethacin nonpareil seeds using Eudragit RL100 and Eudragit RS100 as drug release controlling

resins. The effect of particle size variation of the seeds, and the amounts of Eudragit resins,overcoating with bees wax, on the release rate profile as well as release kinetic of Indomethacin from the seeds were investigated.

EXPERIMENTAL

MATERIALS AND METHODS

Materials:

- Eudragit RL100,RS100(Rhom Pharm,GMBH, Weiterstadt, Germany).
- Indomethacin (Geopharm, Milan, Italy).
- Corn starch USP(FMC Corporation,Philadelphia, PA), USA.
- Bees wax (E. Merk, Darmstadt, Germany).
- Glucose (Food grade).
- Talc (Charles, B. Chrystal Company,Inc., New York, NY).
- Carboxymethylcellulose sodium,BDH (Poole,England).
- Acetone, isopropyl alcohol, chloroform (Analytical grades).

METHODS

1. Nonpareil seeds preparation:

Nonpareil seeds were prepared from a powdered mixture of glucose, carboxymethylcellulose sodium, corn starch, talc and water using the conventional pan coating method as follows:

500 gm glucose finely powdered, 5 gm carboxymethylcellulose sodium and 5 gm corn starch were dry blended and then placed into 8 inch conventional coating pan rotating at 30 rpm. Distilled water was sprayed onto the powder mixture to moisten it as the pan rotated. The seeds formed were

then wetted again by spraying distilled water and then 5 gm talc powder was dusted onto the seeds. After the powder covered the moistened seeds surface uniformly, a stream of hot air was blown to dry the seeds. The step of wetting and dusting the seeds was repeated continuously until the seeds were built up to spheres of desired size. The seeds were then removed from the pan and the size distribution was evaluated by using a sieve analysis technique using a set of USP standard sieves.

Nonpareil seeds having a particle size range of (1.7-1 mm) and (2.38-2 mm) were selected for the preparation of prolonged release Indomethacin Nonpareil seeds.

2. Drug loading and polymer coating of the seeds:

Drug loaded seeds which had Indomethacin impregnated onto them were prepared by placing 100 gm of the selected nonpareil seeds in a coating pan rotated at 50 rpm. The seeds were then wetted by 20 ml (5%) aqueous solution of (CMC Na) solution.20 gm Indomethacin powder were then dusted onto the wetted seeds in 5 gm portions, and the resulting product then hand screened and dried. The cycle was continued until all the amount of Indomethacin were impregnated onto the seeds. The seeds were then dried and assayed for their drug content. The drug loaded seeds were coated by spraying either with Eudragit RL100 or RS100 dissolved in 1:1 isopropanol acetone mixture in a coating pan using a hot stream of air. Different batches were prepared using different concentrations of Eudragit RL100 and Eudragit RS100 ranging from 5-15% W/V.The resultant coated seeds were

dried at 50°C for 24 hours to remove the residual volume of solvent.

3. Wax overcoating of the seeds:

The previously polymer coated seeds were subsequently wax treated using 5% chloroformic solution of Bees wax to improve and control their sustained release character, adopting the previously mentioned procedure.

4. Determination of total drug content:

Total drug content was determined by dissolving accurately weighed portions of each batch in 50 ml methanol. The amount of Indomethacin in the methanolic solution was assayed spectrophotometrically at 265 nm. None of the nonpareil seed components interfered with the drug assay at this wavelength. Duplicate samples were assayed and the mean values reported.

5. Dissolution study:

Dissolution measurements were carried out in a USP dissolution test apparatus, paddle method (Caleva Ltd., Model 85T) using an automated monitoring system which consists of an IBM computer PK 8620 series and PU 9605/60 tablet dissolution system software, Philips UGV, vis NIR single beem spectrophotometer PU 8605/50 eight cell program, Epson LX 850 Printer and Matson-Marlow prestatic pump. An appropriate amount of Indomethacin nonpareil seeds containing 75 mg of Indomethacin was used with 900 ml of phosphate buffer of pH 7.4 at 37.5±0.5°C and at a rotation speed at 50 rpm.

TABLE 1

Particle Size Distribution and Efficiency of Loading Proces In INdomethacin Nonpareil Seeds prepared by the Conventional Pan Coating Method.

Particle size range m.m.	% of non-pareil seeds (1)	Arithmatic mean size (m.m) (2)	Weight size (1x2)	Efficiency of loading process= Actual assay/Theoretical assayx100
2.38-2	21.9	2.19	47.961	65.4
2 -1.7	14.2	1.85	26.27	67.14
1.7 -7	53.1	1.35	71.685	71.23
1 -0.8	1.9	0.9	1.71	75.15
0.8 -0.3	8.9	0.55	4.895	87.031
	100%		152.521	
Mean Particle Diameter (1.525 m.m.)			Average Loading Efficiency (71.38%)	

6. Analysis of the data:

The release data of Indomethacin from the Nonpareil seeds was analyzed according to zero, first-order kinetics and diffusion controlled mechanism.

RESULTS AND DISCUSSION

Table (1) shows the particle size distribution and the efficiency of loading process of Indomethacin on the Nonpareil seeds prepared by the conventional pan coating process. It is clear that the nonpariel seeds

in general exhibited narrow particle size range where 53% of the seeds have a particle size range 1.7-1 mm. The average arithmatic diameter of the seeds was 1525 micron.

The actual drug content, calculated as opposed to the theoretical drug loading, was determined according to the assay described. Particle size range (0.8-0.3 mm) gave 87.03% of indomethacin content compared with 65.4% for particle size range (2.38-2 mm).

Figure (1) represents a cumulative plot of percent of Indomethacin released versus time from Nonpareil seeds having different particle size ranges and coated with different concentrations of either Eudragit RL100 or RS100 in phosphate buffer of pH 7.4 at 37°C. It is evident that coating of Indomethacin loaded Nonpareil seeds with Eudragit RL100 or RS100 resulted in a marked decrease in drug release. The release rate profile of Indomethacin from the coated Nonpareil seeds depend, to a greater extent, on the seeds particle size, type and concentration of the coating material. The results show that the dissolution of Indomethacin from the uncoated seeds is faster than the dissolution of the drug from the coated ones. Ninty five percent of the drug dissolved in 30 minutes where only 16-89% of the total Indomethacin content was released at the end of 7 hours of the coated seeds. The particle size of the seeds affect the rate of Indomethacin release from the coated nonpareil seeds. Pellets having a particle size range of 1.7-1 mm exhibited a smaller diameter and larger surface area. The release of Indomethacin from these seeds was somewhat faster than from the larger seeds which have a particle size range 2.38-2 mm. Similar effect was found by Li et al., (14) who have studied the effect of coating Nonpareil seeds containing Indomethacin with Eudragit S100. These authors found that in ad-

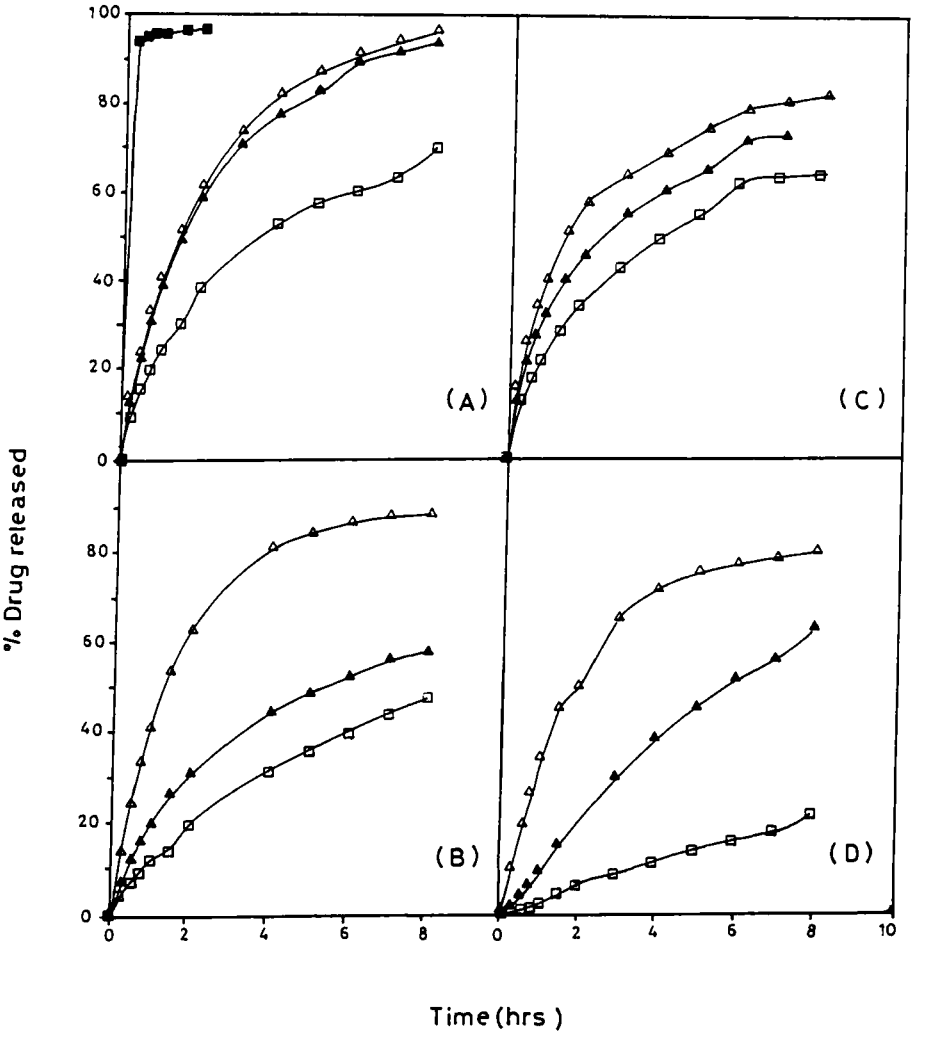

FIGURE 1

Release rate profiles of Indomethacin coated non-pareil seeds in phosphate buffer of pH. 7.4 at 37±0.5°C.

■ Indomethacin noncoated seeds (PS 1.7-1 mm)

△ 5% ▲ 10% □ 15%

A.	Eudragit RS100	PS	1.7-1 mm
B.	" "	"	2.38-2 mm
C.	" RL100	"	1.7-1 mm
D.	" "	"	2.38-2 mm

dition to the surface area consideration, the thickness of the matrix layer may also alter the release rate profile of Indomethacin. In our study, coating of the seeds with different concentrations of either Eudragit RL100 or RS100 produces noticeable change in the release rate profile, where Eudragit RL100 gave more sustaining effect. The difference observed in the drug release from Eudragit coated beeds may be attributed to the difference in the permeability of the Eudragit used. A case which was in accordance with that was reported before (16,17). As the concentration of the coating material increased, a decrease in the release rate of the coated Indomethacin seeds was observed. For instance, at a higher coating level such as 15% coating of Indomethacin Nonpareil seeds (p.s. 1.7-1 mm) with Eudragit RS100 or RL100, released 7.8% and 15.9% of the drug after 30 minutes and 44.5% and 63.5% after 7 hours, respectively. For those seeds having a particle size of 2.38-2 mm, the amounts released were 1.3% and 14.28% after 30 minutes and 16.34% and 62.55% after 7 hours. The integrity of the coating was well preserved through the dissolution experiment, even when the drug was completely released. These results are in agreement with those obtained by Li et al. (14), who stated that, in addition to the decrease in the release rate of the coated seeds at the higher coating levels, the drug was released after a lag time which became larger in proportion to the thickness of the Eudragit coating.

Additionally, to provide further control of the release profiles by increasing the diffusional barrier, the effect of a second overcoat with waxy material was investigated and bees wax was used. Coating of the precoated Indomethacin nonpareil seeds with 5% bees wax was shown to delay the drug release to a greater extent (Fig. 2). This process may be advantageous for those

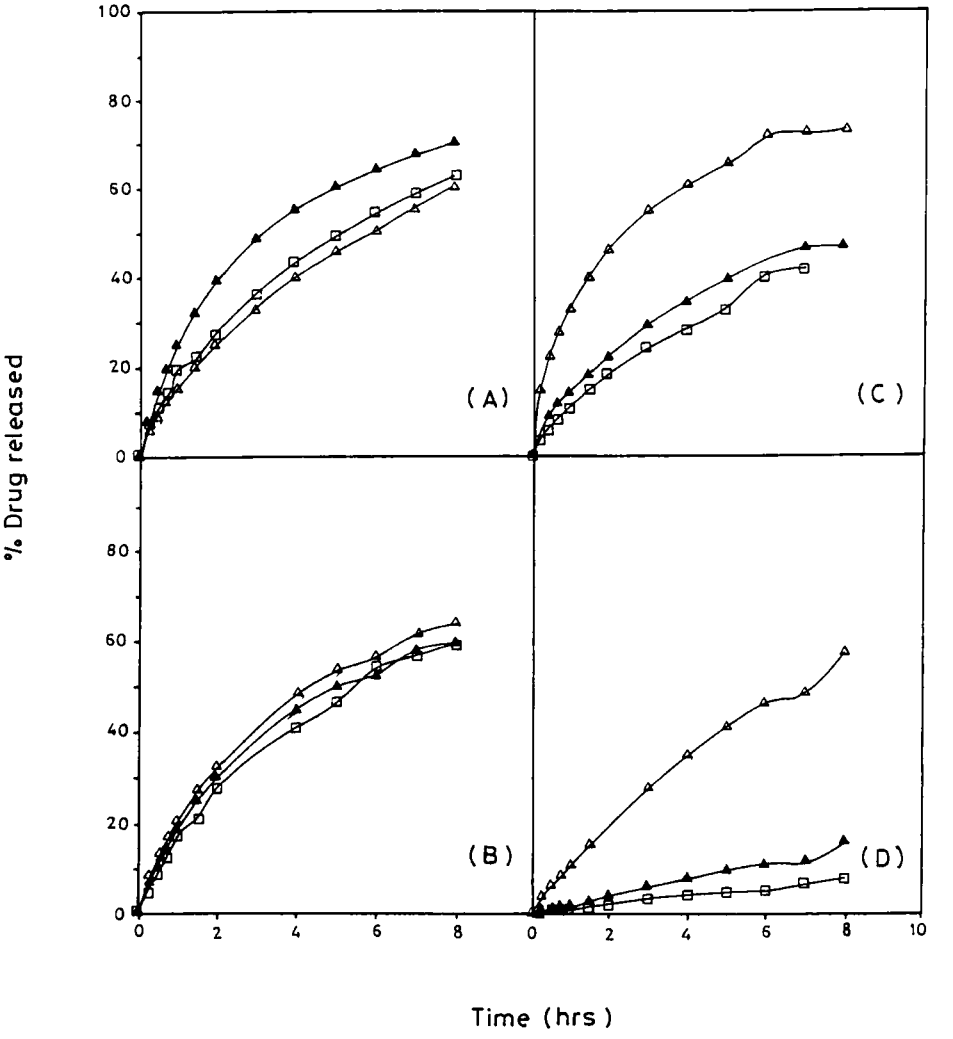

FIGURE 2

Release rate profiles of Indomethacin bees wax overcoated non-pareil seeds in phosphate buffer of pH. 7.4 at 37±0.5°C.

△ 5% ▲ 10% □ 15%

A.	Eudragit	RS100	+	5%	bees	wax	PS	1.7-1 mm
B.	"	"	+	"	"	"	"	2.38-2 mm
C.	"	RL100	+	"	"	"	"	1.7-1 mm
D.	"	"	+		"	"	"	2.38-2 mm

TABLE 2

Comparison of correlation coefficients from in-vitro dissolution data of Indomethacin non-pariel seeds fit to various release models in phosphate buffer of pH 7.4 at 37°C.

Particle size (m.m)		Eudragit RL100(%)			Eudragit RL100%+5% Bees wax			Eudragit RS100(%)			Eudragit RS100+5% Bees wax		
	Conc.(%)/ Release order	5	10	15	5	10	15	5	10	15	5	10	15
2.38-2 (m.m)	Zero(r2)	0.912	0.960	0.968	0.973	0.970	0.9661	0.923	0.910	0.991	0.947	0.991	0.961
	First(r2)	0.965	0.996	0.998	0.9964	0.988	0.9881	0.983	0.988	0.990	0.980	0.990	0.984
	Diffusion(r2) Model	0.970	0.992	0.990	0.9914	0.974	0.979	0.976	0.992	0.987	0.988	0.993	0.993
	Log Q vs Log t(r2)	0.975	0.996	0.995	0.9066	0.990	0.973	0.911	0.991	0.999	0.940	0.984	0.994
	n	0.572	0.490	0.497	0.562	0.510	0.516	0.394	0.502	0.697	0.313	0.547	0.580
1.7-1 (m.m)	Zero(r2)	0.928	0.968	0.989	0.972	0.971	0.982	0.938	0.934	0.969	0.988	0.954	0.984
	First(r2)	0.987	0.988	0.997	0.988	0.989	0.994	0.999	0.997	0.989	0.998	0.992	0.999
	Diffusion(r2) Model	0.978	0.996	0.992	0.996	0.996	0.997	0.984	0.982	0.993	0.999	0.992	0.999
	Log Q vs Log t(r2)	0.978	0.993	0.998	0.996	0.993	0.994	0.990	0.983	0.882	0.913	0.9811	0.998
	n	0.567	0.582	0.673	0.609	0.646	0.703	0.497	0.545	0.498	0.472	0.557	0.634

nonpareil seeds with smaller particle size which release drug rapidly and which can tolerate a significant increase in the size without adverse organoleptic properties. The major disadvantage of this process was that the amount of drug released was much reduced and this makes the process in some cases not applicable to drugs where a high dose is needed to attain maximum therapeutic level.

In order to obtain meaningful information for the release models, the drug release profiles were fitted to various kinetic models. Table (2) summarizes the correlation coefficients for the different release kinetic models of Indomethacin coated nonpareil seeds. Models with higher correlation coefficients were judged to be a more appropriate model for the dissolution data.

The linear relationship existing between the logarithm of the percent drug remaining to be released from the coated seeds and time as well as the relationship between the amount of Indomethacin released with square root of time (Tab. 2) indicating that the drug release model appeared to fit both first order and Higuchi diffusion model (18). Different values of n (release exponent, which indicate the mechanism of release) were observed and ranged between 0.34 to 0.6, thus confirming the diffusion mechanism of Indomethacin release from the Eudragit coated nonpareil seeds.

In conclusion, sustained release Indomethacin coated nonpareil seeds can be prepared successfully by the conventional pan coating method using Eudragit retard or Eudragit retard and bees wax. The release rate can be varied by varying the concentration, type of the coating material as well as the particle size of the seeds.

Rendering the surface of the coated seeds hydrophobic by applying an waxy overcoat decreases the release of Indomethacin significantly.

The release of Indomethacin from the coated nonpareil seeds is dependent upon either the remaining concentration to be dissolved or the square root of time i.e. can be described by both first-order kinetic model and Higuchi diffusion model.

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REFERENCES

1. D.M. Newitt and J.M. Conway-Jones, J.M., Trans. Inst. Chem. Eng. 36, 422 (1958).
2. B. Gajdos, Drug mode Ger., 27(1) 30-34, 36 (1984).
3. A.D. Reynolds. Mfg. Chem. Aerosol. News. 41(6), 40, (1970).
4. G. Rothgang. Acta. Pharm. Technol., 20(1), 39, (1974).
5. M.J. Gamlen, Mfg. Chem., 56(6), 55, 57, 59 (1985).
6. P.J. Harrison, J.M. Newton, R.C. Rowe., J. Pharm. Pharmacol., 37:686-691 (1985).
7. R.E.O'Connor, J. Holinej. J. and J.B. Schwartz., Am.J. Pharm., 156, 80 (1984).
8. S.A. Kaplan, In "Dosage Form Design and Bioavailability", J. Swarbrick, ed., Lea and Febiger, Philadelphia, 1973, p. 20.
9. P.L. Boardman and F. Dudley Hart, Ann. Rhem. Dis., 26, 127 (1967).
10. P. De Haan and C.F. Lerk., Pharm. Weekbl. Sci., 6, 57 (1984).
11. M.J. Gamlen, Chemists and Druggist, 13(56) (1969).
12. E.S. Ghali, G.H. Klinger and J.B. Schwartz. Drug Dev. Ind. Pharm., 15, 1455 (1989).
13. O.M. Al-Gohary, S.S. Abd-El-Hady and N.A. Daabis. Drug Deve. Ind. Pharm., 17(15) 2055 (1991).

14. S.P.Li, K.M. Feld, C.R. Kowarski., Drug Dev. Ind. Pharm., 17(12) 1655 (1991).
15. Ibid, 15(8), 1137 (1989).
16. K. Lehmann, Drug made in Germany, 11, 34 (1968).
17. K. Lehmann, D. Dreher, Ibid, 12, 59 (1969).
18. T. Higuchi, J. Pharm. Sci., 52, 1145 (1963).