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DEVELOPMENT OF MATRIX CONTROLLED RELEASE BEADS BY EXTRUSION-SPHERONIZATION TECHNOLOGY USING A STATISTICAL SCREENING DESIGN

Sanjay R. Goskonda[1], Gregory A. Hileman[1,2], and Sathyanarayana M. Upadrashta[1,3], [1]School of Pharmacy, University of Missouri-Kansas City, Kansas City, MO , [2]Marion Merrell Dow Inc., Kansas City, MO, [3]Bristol-Myers Squibb Company, Evansville, IN

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ABSTRACT

The objective of this study was to develop beads with inherent modified release characteristics requiring no subsequent controlled release coating. Extrusion-spheronization was chosen to accomplish this goal. The model drug was a zwitterion (isoelectric point ~pH 5.2) with poor solubility and low bulk density. Preliminary studies indicated that matrix beads with modified micro-environmental pH would result in sustained release of the drug. A Nica extruder and spheronizer were used to manufacture the beads. A Plackett-Burman screening design was employed to isolate critical variables influencing the bead characteristics and drug release. Variables studied included the type of polymeric dispersion, polymer concentration, acid type, acid concentration, plasticizer content, drug concentration and spheronizing time. Responses evaluated included capsule fill weight, drug release rate, micro-environmental pH, yield and friability. Beads were successfully manufactured according to the screening design and exhibited different dissolution characteristics. Polymer type (Eudragit RS 30 D over Aquacoat ECD-30), polymer concentration and acid concentration significantly retarded drug release. However, increasing acid concentration increased bead friability. In addition to drug concentration, higher polymer concentration, appropriate acid selection and longer residence times afforded maximum capsule fill weights and increased bead density.

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INTRODUCTION

The objective of this study was to develop beads with inherent modified release characteristics, without subsequent controlled release coating. Beads as multiple unit dosage forms are highly preferred [1] over tablets in developing sustained release dosage forms because of their greater predictability and reproducibility of therapeutic effect, as well as lower risk of dose dumping. These ideal bead characteristics are attributed to their highly reproducible gastrointestinal transit rate, both between and within subjects [2]. Conversely, tablet [3] transit rate is heavily dependent on stomach emptying rates and gastrointestinal movements.

Extrusion-spheronization technology was chosen to achieve these goals. Bead production by extrusion-spheronization has been described previously [4, 5, 6]. The main processing steps are dry blending, wet mixing, extrusion of wet granulations into cylindrical extrudate and spheronization of this extrudate, using a spinning serrated plate. Attempts have been made to produce slow release beads by extrusion-spheronization without subsequent coating by other workers [7, 8, 9, 10] but with limited success. Different Avicel products [7], blends of Avicel products [9], Avicel along with waxes [10] and series of release retarding materials [8] have been incorporated into bead formulations to slow the release of drugs. Avicel products with NaCMC content showed slower release in water, attributed to the formation of a gel plug [7, 9] in the USP dissolution basket. The formation of a gel plug is probably due to coalescence of beads in the basket and thus the purpose of multi-unit dosage forms is lost. Bioavailability studies of hydrochlorothiazide pellet formulations consisting of Avicel RC-581 (contains 11% NaCMC) did not suggest slow release *in vivo* [11]. Incorporation of waxes into a microcrystalline cellulose matrix [10] resulted in faster release due to matrix interruption. Thermal treatment of the beads resulted in sustained drug release. Drug loading in all the studies was low (10%). Several materials failed in retarding drug release [8]. Carnuba wax was an exception, again at low drug concentrations. Chitosan and Avicel RC-591 were used as matrix materials for retarding drug release [12]. These experiments involved dissolution studies in both USP paddle and basket methods. Slower release was obtained using the basket method and is probably due to clogging of the basket by the swollen beads. Release was much faster by the paddle method and was attributed to disintegration of the swollen beads. Polymeric dispersions Aquacoat

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ECD 30 and Eudragit RS 30 D were used in combination with Avicel PH-101 or Avicel RC-591 [13] to produce acetaminophen and ibuprofen beads. Ibuprofen release was retarded significantly when formulated at low drug loading (10%) with higher amounts of polymeric dispersion. Avicel RC-591 was an effective aid in successful spheronization at higher drug loads and when greater amounts of polymeric dispersions were used. A recent [14] study indicated that the release of indobufen could be modified using combinations of pH adjusters and polymeric dispersions and employed Avicel PH-101 as spheronizing aid. The extent of slow release was limited (80% released in 4 hours). A few patents in pharmaceutical industry also deal with similar situations [15, 16, 17, 18]. The patented systems were not thoroughly investigated and the application of each was limited.

In the present case, the model drug was zwitterion (isoelectric point ~ pH 5.2), had poor water solubility and low bulk density. Preliminary experiments suggested that sustained release at higher drug loading could be achieved by developing a polymeric bead matrix and modifying its micro-environmental pH to minimize drug solubility. Subsequently experiments were designed to explore the effects of two polymeric dispersions, Aquacoat ECD-30 and Eudragit RS 30 D, on the release characteristics of bead formulations. Other factors studied were acid type (fumaric acid and succinic acid), acid concentration, plasticizer content (acetyltributyl citrate) and residence time in the spheronizer.

Statistical experimental designs are strongly recommended in developing pharmaceutical products whose characteristics are influenced by various formulation and process factors [19]. Screening designs assist in isolating critical factors that affect the desirable product attributes. Insignificant formulation and process variables can be fixed at desired levels or eliminated in later experiments. A Plackett-Burman screening design was employed in this study to isolate the critical factors influencing drug release from the beads. Capsule fill weights, particle size distribution, friability and the micro-environmental pH were the responses studied.

EXPERIMENTAL

Materials

Microcrystalline cellulose (Avicel RC-591, FMC Corporation, Philadelphia, PA) was used as the spheronizing aid. The polymeric dispersions tested were Aquacoat ECD-30 (FMC Corporation, Philadelphia, PA) and Eudragit RS 30 D

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(Rohm Pharm. Tech, Malden, MA). Fumaric acid and succinic acid (Pfizer, New York, NY) were used to alter the pH of the micro-environment. Acetyltributyl citrate (Morflex Chemical Company, Inc, Greensboro, NC) was used as a plasticizer. The model drug (MDL201,040, Marion Merrell Dow Inc., Kansas City, MO) is a zwitterion and was supplied as a fine powder with a mean particle diameter of 10 to 15 microns. It is poorly soluble in water and common alcohols.

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Experimental design

A twelve run Plackett-Burman screening design consisting of seven factors at two levels was set up (Table 1) using PC-based software (Statgraphics, STSC, Inc., MD). Formulation and process variables and the ranges for each to be explored were chosen from the knowledge obtained in preliminary experiments. The factors investigated are listed in Table 2. Avicel RC-591 is a key ingredient for effective spheronization; the formulation was designed to have enough Avicel RC-591 for successful spheronization of beads after adding the maximum possible amount of polymeric dispersion. The NaCMC in Avicel RC-591 acts as binder and aids in effective spheronization at high drug loads. The concentration of Avicel RC-591 was a float variable in the formulation, so its influence cannot be separated from the other tested factors. Extruder and feeder speeds were kept constant in this design. The Plackett-Burman design allows for separation of main effects from two and three factor interactions, but confounds all interactions with each other. Data analysis provides for rank ordering of all variables for each measured response.

Pellet manufacturing

The formulation and operating variables for each batch were fixed as per the Plackett-Burman design (Table 2). Batch size for each formulation was 0.5 Kg. The drug, Avicel RC-591 and acids (fumaric or succinic acid) were blended in a planetary mixer (Hobart N-50, Hobart Corporation, North York, Ontario) at low speed setting. The amount of Avicel RC-591 was a float variable in making the required batch size. Avicel RC-591 varied from 23.5 % to 44.5 % depending on the formulation in the design. Required amounts of the polymeric dispersion (Aquacoat ECD-30 or Eudragit RS 30 D), previously mixed (30 minutes) with acetyltributyl citrate in a beaker using a low shear propeller mixer, were added to the dry blends and mixed in a planetary mixer for an additional five minutes to make wet granulations.

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TABLE 1

Process and Formulation Variables Studied

Factor	Low	High
Formulation		
Polymeric dispersion	Aquacoat ECD-30	Eudragit RS 30 D
Acid type	Succinic acid	Fumaric acid
Polymer concentration	14 %	22 %
Acid concentration	0.5 %	3 %
Drug concentration	40 %	50 %
Plasticizer concentration	1 %	4 %
Spheronization		
Residence time	8 minutes	15 minutes

TABLE 2

Plackett-Burman Screening Design with Seven Variables (randomized runs)

Run	PTYPE	ATYPE	DCONC	PCONC	ACONC	PL-CO	RES-T
1	EURS	FUA	40	22	0.5	1	8
2	AQEC	SUA	40	22	3.0	4	8
3	AQEC	FUA	50	14	3.0	1	8
4	AQEC	FUA	50	22	0.5	4	15
5	AQEC	SUA	40	14	0.5	1	8
6	EURS	FUA	40	22	3.0	1	15
7	EURS	SUA	50	22	0.5	4	8
8	EURS	FUA	50	14	3.0	4	8
9	AQEC	FUA	40	14	0.5	4	15
10	EURS	SUA	40	14	3.0	4	15
11	EURS	SUA	50	14	0.5	1	15
12	AQEC	SUA	50	22	3.0	1	15

KEY:

PTYPE= type of polymeric dispersion

ATYPE = acid type

PCONC = polymer concentration in bead(%)

ACONC = acid content (%)

PL-CO = plasticizer content (%)

RES-T = residence time in spheronizer.

DCONC = drug concentration

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Deionized water was added after the addition of the polymeric dispersions to the mixtures to complete the granulation process in most cases. The amount of water needed was empirically determined. The wet granulations were passed through a Nica extruder (Model E-140, Aeromatic Inc., Columbia, MD) operated at a constant feeder speed (79 rpm), constant extruder speed (30 rpm) and fitted with a 1.2 mm screen. The extrudate was processed in a Nica spheronizer (Model S-320, Aeromatic Inc., Columbia, MD) operated at a plate rotational speed of 900 rpm. The beads were collected after a residence time of 8 or 15 minutes. Beads were dried in a hot air oven at 50^{o} C for 48 hours. The order of manufacture was random.

Bead evaluation

Bead evaluation consisted of particle size analysis by sieving (US. standard sieves) with beads falling in the 14/20 mesh fraction reported as the usable yield. The pH of micro-environment was assessed by measuring the pH of a concentrated suspension (25% w/v) of pulverized beads. In-vitro dissolution studies were performed according to USP Method II in pH 7.5 phosphate buffer at a paddle rotational speed of 100 rpm. Samples were analyzed by UV spectroscopy (300-360 nm). Beads in the 14/20 mesh fraction were utilized for dissolution testing. Release rates were calculated from the slopes of the linear portion of the dissolution profiles, neglecting the burst effect. Capsule fill weights were determined by hand filling size "0" capsule with beads from the 14/20 mesh fraction and are reported as mg of drug per capsule based on the theoretical drug content in each formulation. Friability was determined by subjecting 10 gm samples of the 14/20 mesh fraction with 200 glass beads to abrasion in an Erweka friabilator for 10 minutes. The abraded samples were sieved on a 20 mesh screen for two minutes. The amount retained on the sieve was weighed and % friability calculated.

RESULTS AND DISCUSSION

Range-finding preliminary experiments were conducted before developing the screening design. The observations (Figure 1) aided in choosing the factor levels in the design allowing successful production of beads. The level of drug content (40% or 50%) in the experimental design was selected so that a 250 mg dose could fit into a size "0" capsule. Raw data obtained from the Plackett-Burman screening design are

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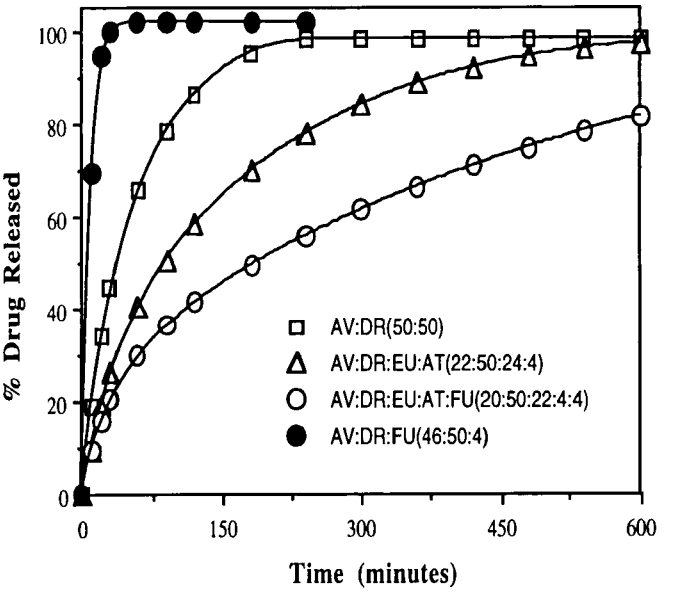

FIGURE 1

Drug release in various bead formulations in preliminary experiments.

Key:	AV	Avicel RC-591	DR	Drug
	EU	Eudragit RS 30 D	FU	Fumaric acid
	AT	Acetyltributyl citrate		

listed in Table 3. Dissolution profiles for different formulations suggested that release of drug could be successfully modified without subsequent coating.

Results from ANOVA tests are shown in Table 4. Only those 'p' values lower than 0.2 are listed for simplification. Drug release was evaluated at 30 minutes and 2 hours to distinguish those beads which disintegrated from those which did not. As expected, highly significant differences in the first 30 minutes disappeared at later time intervals, as the fraction released approached 100%. Release rates were calculated from the slope of the linear portion of the release curve and were independent of the time interval over which they were measured.

From Table 4, it is apparent that both polymer type and concentration significantly affect dissolution. Eudragit RS 30 D retarded drug release more than Aquacoat ECD-30. The average effect on dissolution is shown in Figure 2. Acid

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TABLE 3

Plackett-Burman Response Values

Run	% Released in 30 minutes	% Released in 2 hours	Release rate mg/hr	% Retained mesh 14/20	Capsule fill weight mg	pH*	% Friability
1	30.0	65.9	34.6	97	218.2	4.15	0.7
2	34.8	76.5	34.7	87	213.7	3.85	2.0
3	57.5	98.4	162.0	60	225.2	3.06	3.8
4	43.6	84.2	41.8	61	251.8	3.89	1.0
5	54.2	96.0	121.3	93	203.8	4.28	0.9
6	19.8	44.3	28.7	93	210.1	2.90	0.4
7	27.7	60.6	33.3	96	263.8	4.27	0.4
8	35.5	78.4	37.3	65	238.3	2.78	6.0
9	52.7	94.9	115.3	94	208.2	4.13	1.3
10	32.5	73.1	35.2	96	218.0	3.83	0.9
11	34.5	73.2	33.8	83	273.5	4.60	0.2
12	21.6	52.9	32.7	3	276.6	3.84	3.0

* micro-environment pH

TABLE 4

ANOVA P-Values ($p < 0.2$)

	Release in 30 minutes	Release in 2 hours	Release rate	Capsule fill weight	Yield 14/20 mesh	pH	Friability
Polymer Type	0.008*	0.010*	0.042*	N.S.	0.117	N.S.	N.S.
Acid Type	0.127	N.S.	N.S.	0.031*	N.S.	0.016*	N.S.
Drug Conc.	N.S.	N.S.	N.S.	0.001*	0.044*	N.S.	0.111
Polymer conc.	0.007*	0.005*	0.044*	0.089*	N.S.	N.S.	N.S.
Acid Conc.	0.081*	0.095*	N.S.	N.S.	0.142	0.006*	0.044*
Plasticizer Conc.	N.S.	0.192	N.S.	N.S.	N.S.	N.S.	N.S.
Residence Time	0.117	0.087*	N.S.	0.067*	N.S.	N.S.	0.156

* Highly significant

N.S.-> Not Significant

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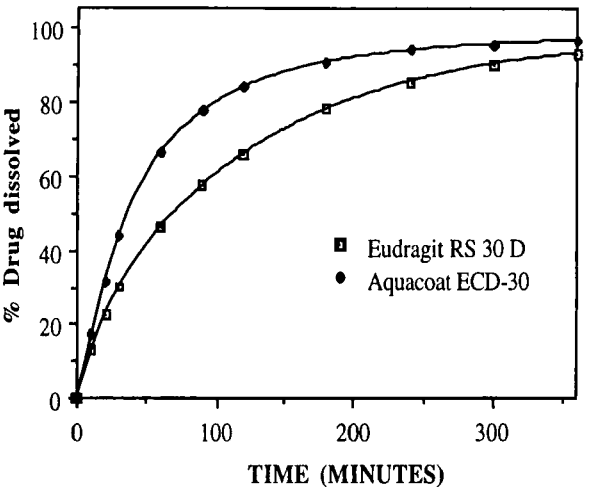

FIGURE 2

Average effect of polymer type on drug dissolution from the bead manufactured in compliance with the screening design.

concentration also affects dissolution regardless of the acid type. Capsule fill weight, which is reported as the calculated mg of pure drug in a capsule, is expectedly affected by changing drug and polymer concentrations. Acid type and to a lesser extent, spheronizing time, also significantly influenced capsule fill weights, probably due to their effects on bead shape and density. Effects of pH were expectedly related to acid type and concentration. Friability measurements, originally included to determine whether or not the uncoated beads could withstand subsequent handling, yielded surprising results. Both acid type and concentration significantly affected friability. Yield of 14/20 mesh beads was followed as an overall indicator of the viability of the process. No significant alterations in bead yield were noted. This is due, in part, to the adjustment of water concentration discussed earlier.

The magnitude and direction of each significant ($p < 0.2$)* effect can be estimated from the model, independently of each other. Table 5 lists the estimated

* This level of significance is used at early screening stages to avoid disregarding marginal process variables after only a few experiments. In analyzing the response surface data, a $p<0.1$ significance level was used.

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TABLE 5
Estimated effects

Variable	% Release in 30 minutes	% Release in 2 hours	Release rate (%/hour)	Capsule fill weight (mg/cap)	Yield 14/20 mesh (%)	pH	Friability (%)
from Ethyl Cellulose to Eudragit	-14.07*	-17.86*	-50.80*	N.S.	22.0	N.S.	N.S.
from Succinic to Fumaric	5.62	N.S.	N.S.	-16.26*	N.S.	-0.62*	N.S.
Drug Conc.	N.S.	N.S.	N.S.	42.84*	-32.0*	N.S.	1.36
Polymer Conc.	-14.87*	-21.58*	-49.86*	11.22	N.S.	N.S.	N.S.
Acid Conc	-6.80	-8.53	N.S.	N.S.	-20.1	-0.84*	1.93*
Plasticizer Conc.	N.S.	6.16	N.S.	N.S.	N.S.	N.S.	N.S
Residence Time	-5.84	-8.86	N.S.	12.53	N.S.	N.S.	-1.16

* Significant $p < 0.2$

N.S.-> Not Significant

change in a measured response as each experimental variable moves from its lowest to its highest values. In the case of discrete variables such as acid or polymer type, the table indicates the direction empirically reported. For example, switching from ethylcellulose (Aquacoat) to Eudragit causes an average reduction in the fraction dissolved at 2 hours of 17.86%, whereas switching from succinic to fumaric acid increases the fraction released at 30 minutes by 5.62%.

In general, higher Eudragit concentrations retarded drug release significantly. The effect of acid type on drug release was not statistically significant. The preliminary experimental results (Figure 1) indicated that fumaric acid in the presence of high polymer (Eudragit RS 30 D) concentrations slowed drug release to a great extent. In most cases beads were intact, after dissolution studies. In the absence of Eudragit RS 30 D, drug was released in less than 30 minutes (Fig 1) as the beads disintegrated. Sodium carboxymethylcellulose (NaCMC), which is

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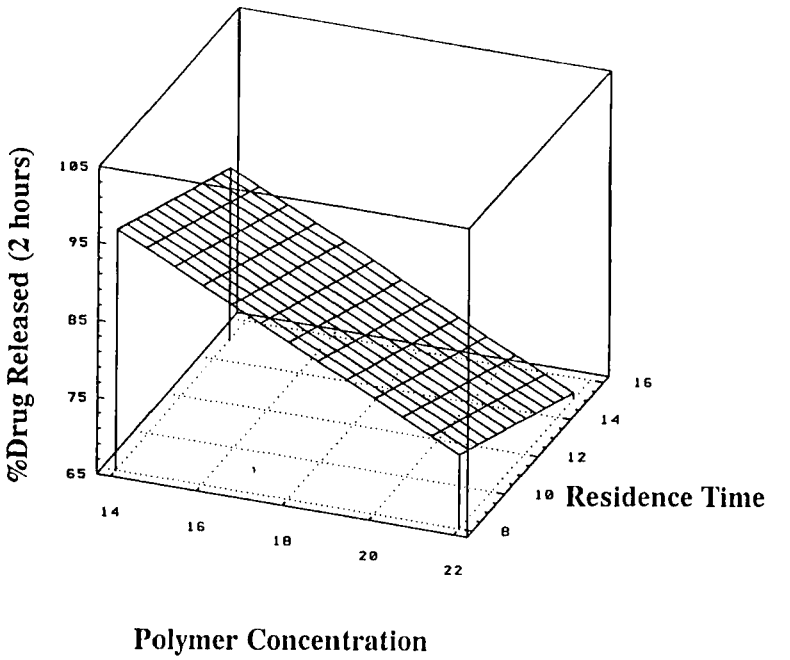

FIGURE 3

Effect of polymer concentration and residence time on drug release.

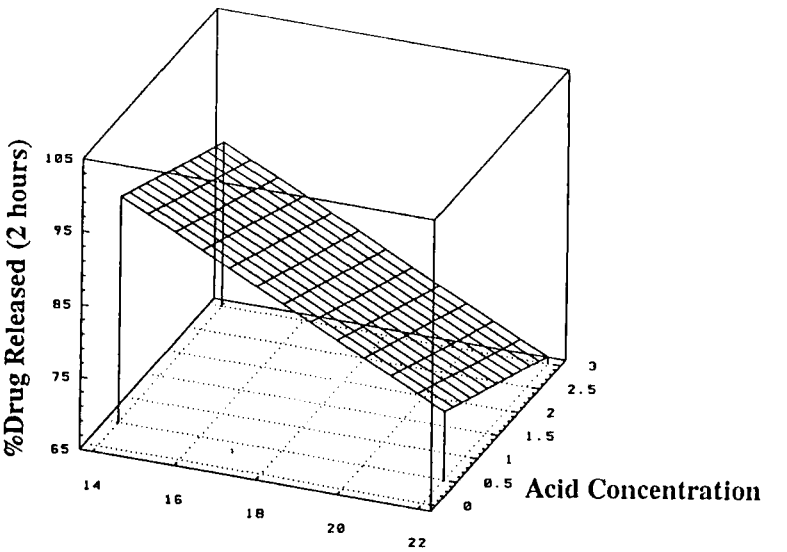

FIGURE 4

Effect of polymer concentration and acid concentration on drug release.

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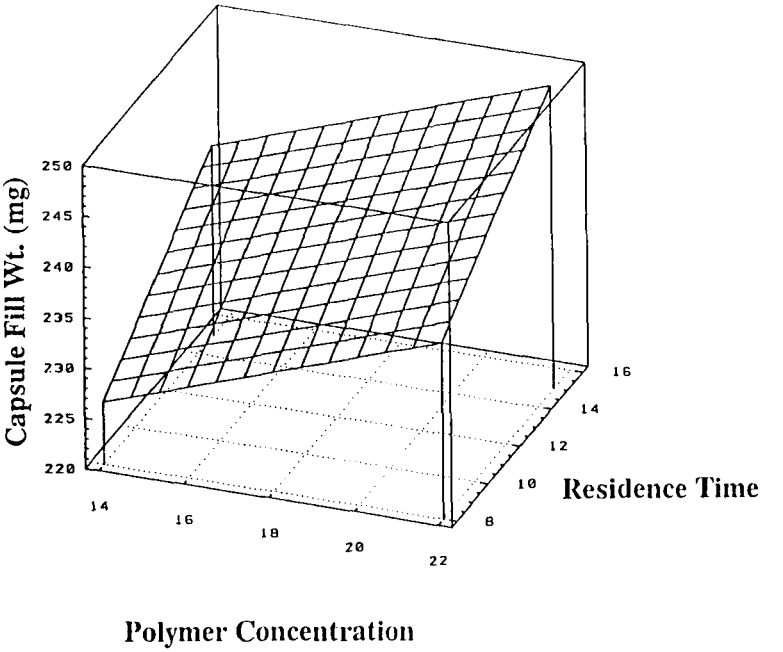

FIGURE 5

Effect of polymer concentration and residence time on capsule fill weight (active).

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present in Avicel RC-591 and serves as a binder, can be converted to the less soluble free acid carboxymethylcellulose (CMC) in sufficiently low pH ranges (Hercules product information). This may have contributed to the increased drug release at 30 minutes noted with the slightly stronger fumaric acid. This is further supported by an increase in friability of the beads with increasing acid concentration. Some of the factors affecting drug release and capsule fill weights are shown in estimated response plots (Figures 3- 5).

Fractional factorial designs can be used to generate limited linear models of the response surfaces in terms of the experimental variables in the design. In the present case, no linear model correlation coefficient (adjusted for the degrees of freedom) exceeded an r^2 value of 0.9. This could be attributed to actual nonlinear relationships between variables and responses, confounding of interaction terms with the main effects which occurs in this and most fractional factorials and/or significant effects caused by factors not included in the design and analysis.

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CONCLUSIONS

Beads were successfully produced in all cases and exhibited different dissolution characteristics, confirming that the concept of producing controlled release beads without subsequent overcoating is feasible. Eudragit RS 30 D in higher concentrations and accompanied by higher acid concentration was effective in retarding drug release. The results indicated that higher drug concentrations (50% loading) with Eudragit RS 30 D as the release modifying matrix material, an organic acid as pH modifier in the bead and Avicel RC-591, would yield a product exhibiting sustained release. With no requirement for subsequent overcoating, the process described would be of economical importance, since it could offer reduced process time and equipment than most conventional processes.

REFERENCES

(1) H. Bechgaard and G. H. Nielsen, Drug Dev. Ind. Pharm., 4, 53 (1978).
(2) H. Bechgaard and K. Ladefoged, J. Pharm. Pharmac., 30, 690 (1978).
(3) H. Bechgaard and K. Ladefoged, J. Pharm. Pharmacol., 33, 791 (1981).
(4) A. D. Reynolds, Manuf. Chem. Aerosol. News, 41, 40 (1970).
(5) J. W. Conine and H. R. Hadley, Drug.Cosmetic.Ind, 106, 38 (1970).
(6) C. W. Woodruff and N. O. Nuessle, J. Pharm.Sci, 61, 787 (1972).
(7) R. E. O'Connor and J. B. Schwartz, Drug Dev. Ind. Pharm., 11, 1837 (1985).
(8) F. Briquet, C. Brossard, J. Ser and D. Duchene, S. T. P. Pharma., 2, 986 (1986).
(9) E. S. Ghali, G. H. Klinger and J. B. Schwartz, Drug. Dev. Ind. Pharm., 15, 1455 (1989).
(10) E. S. Ghali, G. H. Klinger and J. B. Schwartz, Drug. Dev. Ind. Pharm., 15, 1311 (1989).
(11) J. Herman, J. P. Remon, R. Lefebvre, M. Bogaert, G. H. Klinger and J. B. Schwartz, J.Pharm. Pharmacol., 40, 157 (1988).
(12) S. R. Goskonda and S. M. Upadrashta, Drug Dev. Ind. Pharm., (In Press)
(13) S. R. Goskonda, S. M. Upadrashta and G. A. Hileman *American Association of Pharmaceutical Scientists, Midwest Regional Meeting,* 1992, Chicago, IL.

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(14) R. Bianchini, G. Bruni, A. Gazzaniga and C. Vecchio, Drug Dev. Ind. Pharm., 18, 1485 (1992).

(15) C. B. MacFarlane, A. B. Selkirk and M. J. Dey, U. S. Patent 4,940,556 (1990).

(16) J. Heafield, S. T. Leslie, S. T. A. Malkowska and P. J. Neale, U. S. Patent 4, 867, 985 (1989).

(17) J. Valorose, J. Joseph, R. J. Biehl, N. V. Sheth, W. A. Strathy and M. K. Doelling, U. S. Patent 4, 837, 030 (1989).

(18) Y. M. Joshi, W. R. Bachman and N. B. Jain, U. S. Patent 4,808,413 (1989).

(19) G. Stetsko, Drug Dev. Ind. Pharm., 12, 1109 (1986).

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