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SOME FACTORS AFFECTING THE RELEASE OF DRUG FROM MEMBRANE COATED SLOW RELEASE TABLETS

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ABSTRACT

Tablets containing sodium salicylate were prepared by direct compression and coated with ethylcellulose and polyethylene glycol 3350. The effect of drug loading, direct compression carrier type, polymer ratio in the coating solution, pH of the dissolution medium, and agitation speed on the drug release were investigated using the USP XXI paddle method. It was observed that direct compression carriers, ratio of ethyl cellulose to polyethylene glycol, the amount of drug present in the tablet, and agitation speed used did not have any influence on the drug release from coated tablets, while the pH of the dissolution medium (gastric vs. intestinal fluids) was found to affect the drug release.

INTRODUCTION

Controlled release of therapeutically active agents is desirable to increase the half-lives of drugs which are rapidly eliminated and to decrease side-effects associated with drugs. A

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variety of methods exists for preparation of controlled release tablets, most of which involve addition of excipients which retard tablet dissolution or provide a matrix for diffusion of the active drug. There are few methods for preparing tablets which release drugs at a constant rate. Among these are tablets coated with a porous rate controlling membrane (1).

A membrane coated tablet is coated with a water permeable membrane which is insoluble in the gastrointestinal tract. The release of the drug from such membrane coated tablets may be controlled by modifying membrane characteristics. The mechanism by which the membrane coated tablets release the drug involves the penetration of the tablet by gastrointestinal fluid through the pores which dissolves the drug, and diffuses it out. Hence, the diffusion of solution through the rate controlling microporous membrane plays an important role in the release of the drug. Furthermore, the release of the drug will be a function of its solubility, the number and size of the pores formed in the membrane and the membrane thickness (1). Additionally, the fraction of soluble polymer in the coated membrane would be expected to be a determining factor in controlling drug release (2). After the gastrointestinal fluid penetrates the permeable membrane of the coated tablet and dissolves the drug, a constant release may be expected for a water soluble drug since a saturated solution is formed within the tablet. Under such a condition, the concentration of a drug inside the coated tablet will be much higher than outside the tablet, assuming sink conditions are operative. The membrane coated tablet filled with gastrointestinal fluid will pass through the intestinal tract and will finally be eliminated from the body (3).

Ethylcellulose is a polymer that is completely insoluble in water and gastrointestinal fluid and is therefore, by itself, unsuitable for tablet coating (4). Salib *et al* (5) reported on the possible application of inert and pH insensitive ethylcellulose as a potential sustained release coating material for pharmaceuticals. Samuelov *et al* (6) studied the influence of water soluble polyethylene glycol as a film forming agent on the release of drugs dispersed in ethyl cellulose film. The release of drug from such film is reported (7,8) to follow the diffusion process.

Donbrow and Friedman (9) reported that drug release from heterogeneous films, made up of ethyl cellulose and polyethylene glycol 4000, was not influenced by the pH of the dissolution fluid and the permeability of such film remained unchanged in the gastrointestinal tract. This concept of dispersing drug into a film was extended (10) to attempt a zero order release by dispersing the drug in hydroxypropyl cellulose which was then laminated by ethylcellulose film containing various proportions of polyethylene glycol to enhance permeability. The thickness of the drug-free membrane was reported to control the drug release. Kallstrand and Ekman (1) utilized the rate controlling microporous membrane technique and described its practical application. The core tablet was coated with a porous membrane which controlled the release rate. The release of the drug was reported to be zero order and independent of pH within the physiological range.

One objective of this research was to study the feasibility of obtaining a constant drug release from membrane coated tablets using ethyl cellulose and polyethylene glycol 3350 as

membrane coating materials and sodium salicylate as a model drug. Other objectives were to investigate whether intrinsic factors such as the composition of the film, type of excipient (direct compression carrier) used and drug loading; and extrinsic factors such as pH and agitation speed, have any influence on the rate of drug release from a membrane coated tablet.

EXPERIMENTAL

Manufacture of Tablets: Sodium salicylate[a] tablets were prepared using Lactose DT[b] and Di-tab[c] as soluble and insoluble direct compression carriers, respectively. The composition of four tablet formulations is provided in Table I. The ability of the coated tablet to maintain its integrity during the release study was the criterion considered in the selection of tablet constituents and compressional conditions.

Sodium salicylate and magnesium stearate[d] were separately passed through a 40 mesh sieve. A dry blend of sodium salicylate, Avicel pH 102[e] and direct compression carrier was made by a geometric dilution. The combination was mixed in a cube blender at 22 rpm for approximately 20 minutes. Following this, magnesium stearate and Compritol 888[f] were added and mixed for an additional 3 minutes. Five hundred milligrams of this mixture were weighed and compressed into a cylindrical tablet using a ring press at 10 tons hydraulic pressure. Sodium salicylate was incorporated at 10 and 20% level in each of the carriers. The diameter and thickness of uncoated tablets were measured and recorded.

Coating Solutions: To prepare membrane coated tablets, three coating solutions of different polymer ratios (9:1, 8:2 and 7:3 of ethyl cellulose[g] and polyethylene glycol 3350[h]) were prepared by dissolving them in chloroform[i] to make 5% w/v solution. The composition of these coating solutions are provided in Table II.

Membrane Coated Tablets: Tablets were repeatedly coated by carefully dipping them in coating solutions in such a way as to ensure coat integrity and drying at room temperature. Tablets prepared using soluble direct compression carrier (Formulations A and B) were coated using solution containing ethyl cellulose and polyethylene glycol 3350 in a ratio of 8:2 or 9:1. On the other hand, tablets prepared by using insoluble direct compression carrier (Formulations C and D) were coated with a solution containing the same polymers but in a ratio of 8:2 or 7:3. In each case, the coating solution was applied in such a manner that the tablet weight increased

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[b] Sheffield Products, Norwich, NY
[c] Stauffer Chemical Co., Westport, CT
[d] Mallinckrodt Chemical Works, St. Louis, MO
[e] FMC Co., Philadelphia, PA
[f] Gattefosse Co., Elmsford, NY 10523
[g] Berry and Withington Co., Cambridge, MA
[h] Fisher Scientific Co., Fair Lawn, NJ
[i] Fisher Scientific Co., Fair Lawn, NJ

TABLE I

COMPOSITION OF TABLET FORMULATIONS

INGREDIENTS (%)	FORMULATIONS			
	SOLUBLE DIRECT COMPRESSION CARRIER		INSOLUBLE DIRECT COMPRESSION CARRIER	
	A	B	C	D
Sodium Salicylate	10.0	20.0	10.0	20.0
Lactose DT	83.8	73.8	-	-
Di-tab	-	-	83.8	73.8
Avicel pH 102	5.0	5.0	5.0	5.0
Magnesium Stearate	0.2	0.2	0.2	0.2
Compritol 888	1.0	1.0	1.0	1.0

TABLE II

COMPOSITION OF COATING SOLUTIONS

POLYMER RATIO	ETHYLCELLULOSE (g/100 mL)	POLYETHYLENE GLYCOL 3350 (g/100 mL)
9:1	4.5	0.5
8:2	4.0	1.0
7:3	3.5	1.5

by 200 mg. This ensured the integrity of the coating membrane. The tablet diameter and thickness of the membrane coated tablet were measured and recorded.

Dissolution Fluids: The dissolution fluids employed were distilled water and simulated gastrointestinal fluids (11) of pH 1.2 and 7.5 without enzymes.

Assay: Standard Beer's law curves over a concentration range of 20-200 mg/L were prepared for sodium salicylate in each dissolution fluid. The assay procedure described by Jambhekar and Cobby (12) was used to analyze sodium salicylate.

Release Study: Drug release was determined using the USP dissolution Apparatus 2 (paddle method) with 500ml of dissolution fluid (37 $\pm$ 0.5° C) at an agitation speed of 50 rpm. The dissolution media used in the study were simulated GI fluids (pH 1.2 and 7.5) and distilled water. At suitable time intervals, a 5mL sample was withdrawn from each dissolution flask and replaced with an equal volume of fresh dissolution fluid. The samples were assayed, following appropriate dilutions, and the cumulative mass of drug released was determined. At the end of the each study, tablets were removed, ground, and assayed to determine the residual drug content. To study the effect of agitation speed, an additional speed of 25 rpm was used.

Calculations: The percentage of drug released at each sample time was calculated as the ratio of the mass of drug released at each sample time to the total drug content of the tablet multiplied by 100. The total drug content is the sum of the cumulative mass of drug released at the last sample time and the residual content. The drug release profile for any formulation was obtained by plotting cumulative percent drug released against time. The release rate constant (K) was obtained from the slope of the line.

RESULTS AND DISCUSSION

Tablet Parameters: The tablet diameter and thickness of uncoated and coated tablets are reported in Table III. The small standard deviation in the measurements of coated tablets indicate the uniformity in the applied membrane coat.

Total Assay: The means of the total assays for sodium salicylate in various formulations tested are reported in Table IV. The results reported indicate the mass of drug and percent of theoretical amount present per tablet. The small standard deviation indicates the uniform distribution of the drug in the mixtures.

Effect of Drug Loading: An example of the mean release profiles obtained using water as a dissolution fluid is shown in Figure 1. The computed release rate constants for the formulations tested are summarized in Table V. Formulations containing Di-Tab and Lactose DT as direct compression carriers and coated with a polymer membrane ratio of 8:2 showed no difference in rate constant as a function of drug concentration. In support, there are studies (8,10) reporting that the rate constant should be independent of the drug loading per tablet.

Effect of Compression Carrier: The release profiles in water obtained for 10% formulations prepared using two direct compression carriers are shown in Figure 2. The computed mean

TABLE III

DIMENSIONAL PARAMETERS FOR UNCOATED AND COATED TABLETS

PARAMETERS	UNCOATED TABLET[a]	COATED TABLET[a]	COAT THICKNESS
Diameter (mm)	13.725 ± 0.071	14.920 ± 0.276	0.598
Tablet Thickness (mm)	2.267 ± 0.301	3.813 ± 0.625	0.773

[a] mean ± SD of 20 determinations

5 tablets for each formulation

TABLE IV

SUMMARY OF TOTAL ASSAY FOR SODIUM SALICYLATE TABLETS

		TOTAL ASSAY	
FORMULATION	% DRUG	mg/500 mg TABLET[a]	% THEORETICAL
A[b]	10	48.014 ± 2.006	96.03
B[b]	20	99.297 ± 1.083	99.30
C[c]	10	47.611 ± 3.571	95.22
D[c]	20	97.333 ± 1.495	97.33

[a] mean ± SD of 3 determinations

[b] contains Lactose DT

[c] contains Di-tab

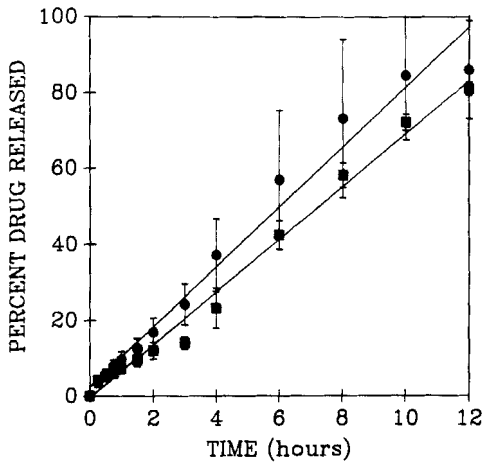

FIGURE 1

Cumulative Percent of Sodium Salicylate Released from Tablets Coated with Ethylcellulose: PEG 3350 in a Ratio of 8:2; Distilled Water of pH 5.9; Agitation Speed, 50 rpm.
KEY: (●) Formulation A
(■) Formulation B

TABLE V

EFFECT OF DRUG LOADING ON DRUG RELEASE

FORMULATION	POLYMER RATIO OF COATING SOLUTION	K[a] (%/hr)	SIGNIFICANCE LEVEL
A	9:1	7.134 ± 0.667	$p<0.01$
B	9:1	3.754 ± 0.588	
A	8:2	7.368 ± 0.504	NS[b]
B	8:2	7.999 ± 1.947	
C	8:2	6.465 ± 0.821	NS[b]
D	8:2	6.212 ± 0.858	
C	7:3	4.743 ± 0.966	NS[b]
D	7:3	5.939 ± 0.784	

[a] mean ± SD of 4 determinations

[b] NS ($p<0.05$)

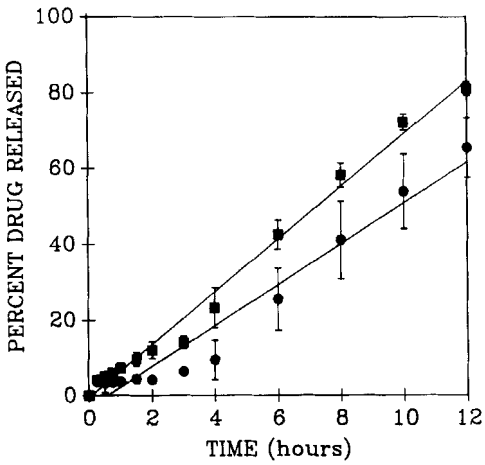

FIGURE 2

Cumulative Percent of Sodium Salicylate Released from Tablets Coated with Ethylcellulose: PEG 3350 in a Ratio of 8:2; Distilled Water of pH 5.9; Agitation Speed, 50 rpm.
KEY: (●) Formulation A
(■) Formulation C

TABLE VI

EFFECT OF DIRECT COMPRESSION CARRIER ON DRUG RELEASE

FORMULATION	POLYMER RATIO OF COATING SOLUTION	K[a] (%/hr)	SIGNIFICANCE LEVEL[b]
A	8:2	7.368 ± 0.504	NS
B	8:2	6.465 ± 0.821	NS
C	8:2	7.999 ± 1.947	NS
D	8:2	6.212 ± 0.858	NS

[a] mean ± SD of 4 determinations

[b] NS ($p<0.05$)

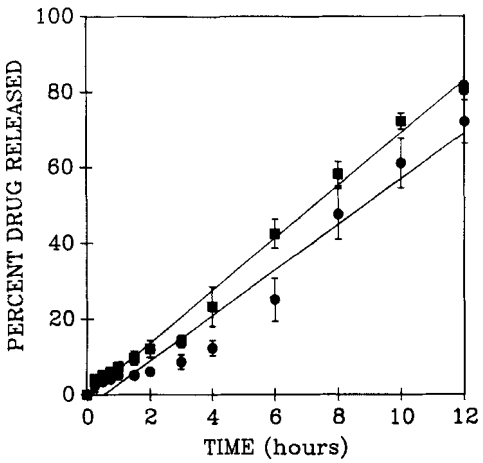

FIGURE 3

Cumulative Percent of Sodium Salicylate Released from Tablets Coated with Ethylcellulose:
PEG 3350 in Ratios of 8:2 and 9:1; Distilled Water of pH 5.9;
Formulation A; Agitation Speed, 50 rpm.
KEY: (■) Polymer Ratio 4:1
(●) Polymer Ratio 9:1

values of the release rate constant (K) for these formulations are summarized in Table VI. It is clear from this that the type of direct compression carrier used in the formulation of tablet did not have any effect on drug release. This may be explained on the basis that the diffusion of the drug through a membrane is *more important than the type of carrier used. Perhaps the type of carrier used may influence the rate at which the drug dissolves inside the membrane coated tablet; however, it is the nature of the membrane that controls the diffusion of a drug into the external dissolution fluid.

Effect of Polymer Ratio: The release profiles in water obtained for 10% drug/lactose membrane tablets coated using various polymer ratios are shown in Figure 3. The computed mean values of the release rate constant (K) are summarized in Table VII. The plot indicates that increasing the ratio of ethyl cellulose to polyethylene glycol did not change the release rate of sodium salicylate from the membrane coated tablets. Earlier studies (6,9,13) have shown that increasing the ethyl cellulose content of the membrane decreased the release rate. The results obtained in this study, however, do not agree with previously reported studies. It is postulated that perhaps a critical mass of ethyl cellulose may be required to cause a decrease in release rate. The amount of ethyl cellulose used in the polymer solution appeared to be less than the critical mass.

TABLE VII

EFFECT OF POLYMER RATIO ON DRUG RELEASE

FORMULATION	POLYMER RATIO OF COATING SOLUTION	K[a] (%/hr)	SIGNIFICANCE LEVEL
A	9:1	7.134 ± 0.667	NS[b]
A	8:2	7.368 ± 0.504	
B	9:1	3.754 ± 0.588	p<0.01
B	8:2	7.999 ± 1.947	
C	8:2	6.465 ± 0.821	p<0.05
C	7:3	4.743 ± 0.966	
D	8:2	6.212 ± 0.858	NS[b]
D	7:3	5.939 ± 0.784	

[a] mean ± SD of 4 determinations

[b] NS (p<0.05)

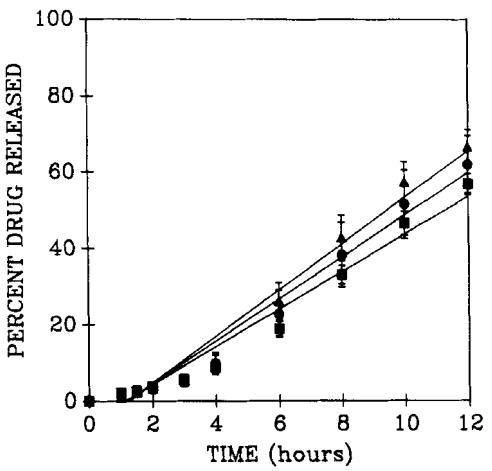

FIGURE 4

Cumulative Percent of Sodium Salicylate Released from Tablets Coated with Ethylcellulose: PEG 3350 in a Ratio of 8:2; Formulation D; Agitation Speed, 50 rpm.
KEY: (■) Simulated Gastric Fluid of pH 1.2
(●) Distilled Water of pH 5.9
(▲) Simulated Intestinal Fluid of pH 7.5

TABLE VIII

EFFECT OF pH OF THE DISSOLUTION FLUID ON DRUG RELEASE

FORMULATION	POLYMER RATIO OF COATING SOLUTION	pH OF DISSOLUTION MEDIUM	K[a] (%/hr)	SIGNIFICANCE LEVEL
D	8:2	5.9[b]	6.212 ± 0.858	NS[c]
D	8:2	1.2	5.597 ± 0.340	
D	8:2	5.9	6.212.± 0.858	NS
D	8:2	7.5	6.855 ± 0.481	
D	8:2	1.2	5.597 ± 0.340	p<0.01
D	8:2	7.5	6.855 ± 0.481	

[a] mean ± SD of 4 determinations

[b] distilled water

[c] NS (p<0.05)

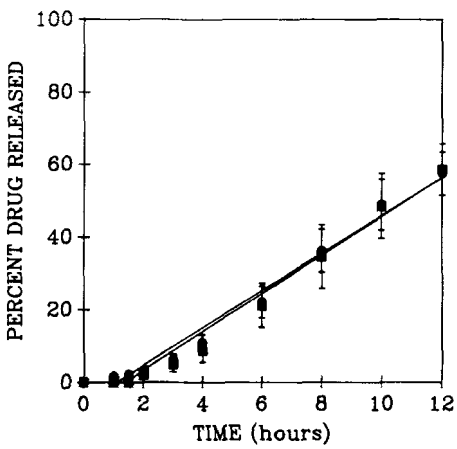

FIGURE 5

Cumulative Percent of Sodium Salicylate Released from Tablets Coated with Ethylcellulose:
PEG 3350 in a Ratio of 7:3; Distilled Water of pH 5.9;
Formulation D;
KEY: (■) Agitation Speed, 25 rpm.
(●) Agitation Speed, 50 rpm.

TABLE IX

EFFECT OF AGITATION SPEED ON DRUG RELEASE

FORMULATION	POLYMER RATIO OF COATING SOLUTION	AGITATION SPEED (rpm)	K[a] (%/hr)	SIGNIFICANCE[b] LEVEL
D	7:3	25	5.477 ± 0.402	NS
D	7:3	50	5.939 ± 0.784	

[a] mean ± SD of 4 determinations

[b] NS ($p<0.05$)

Effect of pH on Drug Release: Figure 4 illustrates an example of the mean profiles obtained in various dissolution media. The computed mean values of the release rate constant (K) for the formulations tested are summarized in Table VIII. The pH of the dissolution fluid had some effect on the drug release rate. The significant ($p<0.01$) increase in release rate was observed between pH 1.2 and 7.5. This may be attributed to pH dependent solubility characteristics of sodium salicylate. In support of this, there is a study (12) which reports that the release of drug is influenced by the pH of the dissolution fluid when a drug exhibits pH dependent solubility characteristics. On the other hand, it has been reported (12) that the release of a drug from a nondisintegrating plastic matrix tablet is quite insensitive to pH differences of dissolution fluids. Furthermore, it has also been reported (11) that when double layered porous film was applied, the dissolution fluid penetrated the membrane and was able to change the degree of ionization of salicylic acid, which increased the release rate.

Effect of Agitation Speed on Drug Release: The release profiles in water obtained for 20%/Di-tab formulation at agitation speeds of 25 and 50 rpm are shown in Figure 5. The computed mean values of the release rate constant (K) are reported in Table IX. From the plots and the results of the rate constant, it is clear that agitation speed had no significant effect on the drug release for the conditions studied. In other studies, Jambhekar and Cobby (12) and Timko and Lordi (14) have reported flow rate and agitation rate independent drug release from nondisintegrating matrix tablet and coated pellets. Flynn *et al* (15) reported that stagnant diffusion layer will have a significant effect on the release if a drug exhibits low aqueous solubility. The results obtained in this study indicate that the drug transport from membrane coated tablet is solely determined by the membrane controlled permeation process when the effect of the stagnant diffusion layer surrounding the membrane coated tablet is negligible.

CONCLUSIONS

The results obtained indicate that it is possible to produce membrane coated tablets which will release the drug at a constant rate. Furthermore, results suggest that a change in drug

loading, the type of direct compression carrier, the ratio of membrance-forming polymer ratios, and the dissolution agitation speed had no significant effect on the release rate of drug from membrane coated tablets; however, the pH of the dissolution medium was found to affect the release rate, especially comparing pH 1.2 and 7.5.

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