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THE IN-VITRO STUDY OF SUSTAINED RELEASE ASPIRIN TABLET WITH POLYETHYLENE RESIN AS INSOLUBLE MATRIX

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A method for sustained release aspirin tablet was developed by using polyethylene resin as insoluble matrix and ethylcellulose as a binding agent. The effect of pressure and binding agent such as ethylcellulose on release rate of aspirin was determined. The degradation of aspirin in sustained release tablets was also studied.

INTRODUCTION

The ever increasing use of sustained release medication has stimulated pharmaceutical research to develop better parenteral and oral preparations. All such preparations are intended to release the active component gradually and continuously over an extended period of time to ensure uniform optional blood and tissue levels. At the same time this also necessitates the avoidance of unnecessary high and low blood levels [1]. Blythe [2] described the technique to produce sustained release of drugs in oral preparations. This type of preparation consists of capsules containing hundreds of differentially coated small pellets of drug which break down and release amounts necessary to prolong the response. With the invention of the multiple layer tablet compression machines it has become possible to make sustained release tablets with more than one layer. Halpern and his co-workers [3] have reported the preparation of quinidine galacturonate by mixing polygalacturonic acid and quinidine base in hydroalcoholic solution. Davies and Gloor [4] reported the preparation of sustained release tablets from the formulations containing hydroxypropylcellulose as binder. Maney and his co-workers [5] prepared sustained-release aspirin tablet by using polyvinyl chloride as a matrix and tested *in-vitro* by chemical determination of liberated salicylate.

Several chemical substances have been applied as matrix such as polymers and co-polymers of acrylates, polyethylene, polyvinyl chloride or acetate and aluminium monostearate. The drug is intimately incorporated in a matrix, from which it is eventually released by diffusion through numerous small pores and capillaries.

Brodie and co-workers [6] studied the absorption of drugs in the rat and in man. They elucidated the concept that the barrier between the gastrointestinal lumen and the blood has the characteristics of a lipoidal membrane permeable to oil-soluble material in an unionized form. Cooper and Lazarus [7] have stated that in addition to lipid solubility, the ability of a drug to combine with protein may also be an important factor which effects absorption. G. Levy [8] has reported that the major site of absorption of aspirin appears to be proximal portion of the small intestine and this is so because intestinal fluids, by reason of their higher pH would bring about much faster dissolution of aspirin than gastric fluids. The purpose of this *in-vitro* study was to develop and evaluate sustained release aspirin tablets using polyethylene resin as an insoluble matrix and employing ethyl cellulose as a binding agent in different proportion. The effect of compactness on the release rate of aspirin was also investigated.

MATERIALS AND METHODS

Preparation of Tablets

(a) *Materials.* Aspirin (No. 80 mesh), polyethylene resin (No. 80 mesh), ethylcellulose, acetone, Hobart Mixer, Twin-shell Dry Mixer, Stokes Single Punch Machine and Strong-Cobb Hardness Tester.

(b) *Procedure.* Sustained release tablets were prepared by incorporating aspirin (600 mg) and polyethylene (40 mg) for each tablet. The aspirin and polyethylene were mixed thoroughly in the twin-shell dry mixer for 20 min and then granulation was done in the Hobart mixer using 1%, 3% and 5% ethylcellulose solution in acetone in order to obtain different binding strength in the granules. The granulation was passed through a No. 20 screen. After drying, the granules were again passed through No.20 screen

and mixed with 1% talc as a lubricant and compressed on the Stokes Single Punch Machine using 7/16-in dia punch. The tablet hardness was maintained between 5–7 kg (measured by Strong-Cobb Hardness Tester).

Determination of Release Rate by In-Vitro *Method*

(a) *Reagents.* Ferric nitrate solution (1% ferric nitrate in 1% nitric acid), 10% potassium hydroxide solution, conc. hydrochloric acid, pH indicator papers, simulated gastric fluid (U.S.P.) and simulated intestinal fluid (U.S.P.).

(b) *Equipment.* Souder and Ellenbogen rotating bottle apparatus with speed of 40 rev/min; Spectronic 20 with round cells and 75 ml bottles with screw cap.

(c) *Procedure.* Samples for the determination of release rate were taken at random from each batch of the tablets and one tablet alongwith 300 mg of powdered aspirin (No. 80 mesh), being added as an initial dose, was placed in a 75-ml bottle. Simulated gastric fluid (60 ml) at pH 1.2 was added and the bottle was rotated in the apparatus at 40 rev/min. at a temperature of $37^{\circ} \pm 2^{\circ}$ for 1 hr. The liquid from the bottle was collected in a 100-ml volumetric flask leaving the undissolved portion in the bottle which was rinsed with 15 ml of distilled water. The washing was added to the contents of the flask.

Simulated intestinal fluid (60 ml) at pH 4.5 was added to the bottle containing the core and bottle was rotated for 1 hr then the fluid was collected in the same manner as described before.

Similarly, simulated intestinal fluid with pH 6.9, 7.2 and 7.5 were added in the bottle and rotated for different intervals of time. At each time the fluid was collected as before.

The method used for the determination of total salicylate present in each volumetric flask was that of Pankratz and Bandelin [9].

Effect of Compactness

For the purpose of this study the granules were prepared by using 5% ethylcellulose solution in acetone. The granules were passed through No. 20 screen lubricated with 1% talc and compressed on the Stockes Single Punch Machine using 7/16-in dia punch at pressures of 6±1 and 10±1 kg.

The procedure for evaluation of *in-vitro* release was the same as described above.

Stability of Aspirin

Sustained release aspirin tablets prepared by using 5% ethylcellulose solution in acetone were kept at 45° for 3 days. Tablets were then assayed for the determination of free salicylic acid as described below:

Assay Procedure. Weighed and powdered 20 tablets. A portion of 0.3 g was accurately weighed and transferred to a 50-ml volumetric flask. It was dissolved in 10 ml of ethyl alcohol and the solution was immediately filtered. Then added 5 ml of freshly prepared ferric nitrate reagent and adjusted the volume to exactly 50 ml. The absorbancy of this solution was determined on Spectronic 20 at 525 mμ. The amount of free salicylic acid was calculated with the help of a standard curve of salicylic acid.

RESULTS AND DISCUSSION

Table 1 and Fig. 1 show the *in-vitro* release of aspirin from tablets prepared with different amounts of ethylcellulose in acetone solution. The onset increase in release rate is

Table 1. Release of aspirin tablets* with different amount of ethylcellulose.

Simulated fluid	pH	Time (hr)	Mean† av.mg.	Mean% release	Mean Cum.
Tablet with 1% ethylcellulose					
Gastric	1.2	1	349.0	38.8	38.8
Intestinal	4.5	1	123.0	13.5	52.3
Intestinal	6.9	2	167.0	18.6	70.9
Intestinal	6.9	1	71.0	7.9	78.8
Intestinal	7.2	2	123.4	13.7	92.5
Intestinal	7.5	1	50.0	5.5	98.0
Tablet with 3% ethylcellulose					
Gastric	1.2	1	343.0	38.2	38.2
Intestinal	4.5	1	114.0	12.7	50.9
Intestinal	6.9	2	151.0	16.8	67.7
Intestinal	6.9	1	67.6	7.5	75.2
Intestinal	7.2	2	120.0	13.3	88.5
Intestinal	7.5	1	46.0	5.1	93.6
Tablet with 5% ethylcellulose					
Gastric	1.2	1	337.4	37.5	37.5
Intestinal	4.5	1	102.5	11.4	48.9
Intestinal	6.9	2	136.0	15.0	63.9
Intestinal	7.2	2	113.2	12.5	83.0
Intestinal	7.5	1	43.0	4.8	87.8

* Each tablet contain 600 mg of aspirin.

† Mean average is the mean of eight determinations.

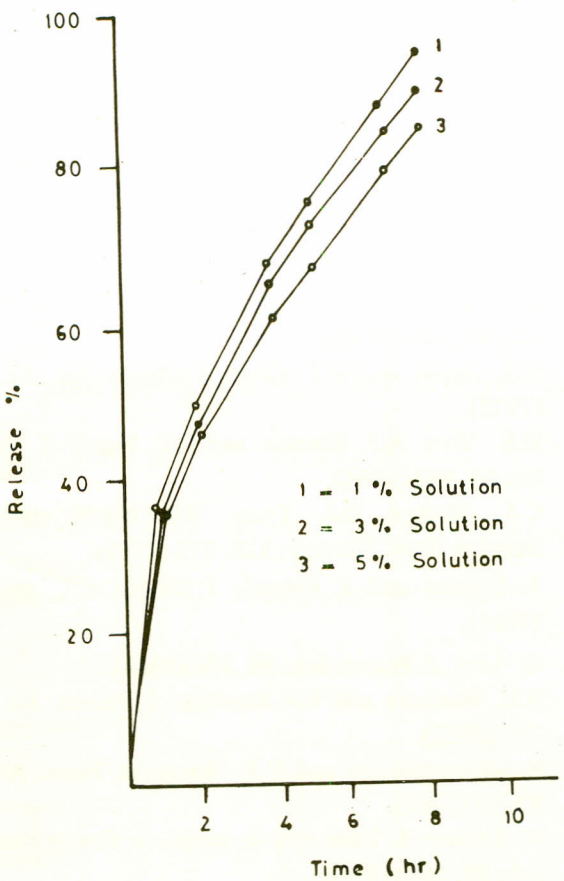

Fig. 1. Precentage release of aspirin tablets with different amounts of ethylcellulose versus time.

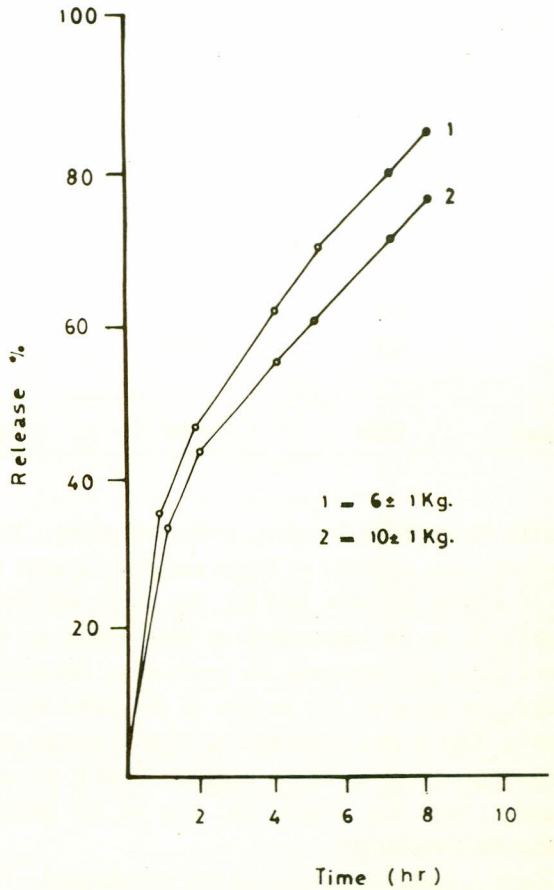

Fig. 2 Percentage release of aspirin tablets with different hardness versus time.

Table 2. Release of aspirin tablets with different hardness.

Simulated fluid	pH	Time (hr)	Mean* av.mg.	Mean% release	Mean Cum.
Tablet with 6±1 kg					
Gastric	1.2	1	337.4	37.5	37.5
Intestinal	4.5	1	102.5	11.4	48.9
Intestinal	6.9	2	136.0	15.0	63.9
Intestinal	6.9	1	61.0	6.6	70.5
Intestinal	7.2	2	113.2	12.5	83.0
Intestinal	7.5	1	43.0	4.8	87.8
Tablet with 10±1 kg					
Gastric	1.2	1	315.0	35.0	35.0
Intestinal	4.5	1	90.0	10.1	45.1
Intestinal	6.9	2	112.4	12.6	57.7
Intestinal	6.9	1	52.4	5.8	63.5
Intestinal	7.2	2	97.3	10.8	74.3
Intestinal	7.5	1	43.0	4.7	79.0

* Mean average determination is the mean of eight determinations.

attributed to the addition of the initial dose without being incorporated with the sustained release aspirin tablet. The comparative study shows that an increase in quantity of the binding agent provides a release rate of longer duration [10]. This is due to the fact that granules acquire a more binding strength which hinders the release of the drug.

Table 2 and Fig. 2, represent the effect of compactness on release rate of sustained release tablets prepared with the same amount of binding agent, but compressed at different pressures. The amount of pressure applied to the tablets exhibits remarkable effect on the release rate of aspirin. The soft tablet releases more of drug due to leaching action. The simulated fluid enters the drug matrix through the loose pores and cracks, and dissolve the drug. In relatively hard compressed tablets, the penetration of the fluid becomes difficult due to lack of void spaces. The dissolution rate decreases with increasing hardness [11]. The nature of the binder also effects the hardness of the table [12].

During the development of sustained release tablets, it was observed that the particle size of the polyethylene resin had an important effect on the compression of the tablets. Since the polyethylene resin is a hard plastic

Table 3. Amount of free salicylic acid in sustained release aspirin tablets at 45°.

No. of assays	Amount of aspirin in mg/tablet	Amount of salicylic acid in mg/tablet	Percentage
1	600	2.41	0.40
2	600	2.61	0.43
3	600	2.64	0.44
Average	600	2.55	0.42

material, its particles, therefore, possess elasticity. It has been found that elasticity of bigger particles is greater than that of smaller particles, and for this reason the former are difficult to be compressed as they return to their original shape and size soon the pressure on the tablet is released. On doing so, the texture of the tablet becomes distorted. This is also attributed to what is known as rebounding power of an elastic material. Thus it is experimentally found that smaller the size of the particles, better is the compression.

Table 3 shows the amount of free salicylic acid present in sustained release aspirin tablets after being kept at 45° for three days. The amount of free salicylic acid was estimated with the help of a standard curve of salicylic acid.

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