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[54] **DRUG FORMULATIONS**

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[51] **Int. Cl.** **A61j 3/07**

[58] **Field of Search** 424/37, 361, 362

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[57] **ABSTRACT**

Method for improving the rate of release of physiologically active agents from capsules, and pharmaceutical compositions adapted for filling into capsules, said capsules filled with such compositions having improved rates of release of the physiologically active agent therefrom.

5 Claims, No Drawings

DRUG FORMULATIONS

BACKGROUND OF THE INVENTION

1. Field Of The Invention

This invention relates to pharmaceutical dosage forms. More particularly, this invention relates to a method for improving the rate of release of physiologically active agents from pharmaceutical capsules, and to pharmaceutical compositions adaptable for filling into such capsules, such capsules filled with such compositions having improved active agent release rate characteristics.

2. Discussion of the Prior Art

Among the various ways of orally administering a physiologically active agent to humans, the use of a two-piece capsule as a carrier for a unit dose of such active agent is one of the most common. The two-piece capsule is normally made of gelatin, but other materials, such as methylcellulose and calcium alginate, which will dissolve in the gastro-intestinal tract and which are non-toxic can also be used.

The rate of release of a physiologically active agent from the capsule is affected by a number of parameters including the disintegration time of the capsule shell, the packing density of the materials in the capsule, the particle size of the materials and the nature of the active agent and the various diluents normally present to aid in obtaining accurate and uniform dosage in the capsule filling operation. While these parameters can frequently be optimized for any given pharmaceutical compositon so as to achieve as quick a release of the physiologically active agent as possible, it often happens that many such compositons show a relatively slow rate of release of the active agent and/or the rate of release is adversely affected by prolonged storage times, especially if stored at elevated temperatures.

Accordingly, it is an object of the present invention to provide a method of improving the rate of release of a physiologically active agent from a capsule.

It is a further object of this invention to provide pharmaceutical compositions adapted for filling into capsules and capsules filled with such compositions having improved active agent release properties.

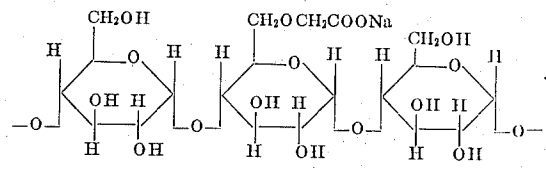
SUMMARY

It has now been discovered that the commingling of an alkali metal carboxymethyl starch, in an amount of from about 2 to about 65 percent by weight, based on the weight of a physiologically active agent, with said active agent provides a pharmaceutical composition adapted for filling into capsules which, when filled into such capsules, provides a pharmaceutical dosage form having improved active agent release rates.

DESCRIPTION OF THE PREFERRED EMBODIMENT

The useful process of this invention comprises commingling an alkali metal carboxymethyl starch and a physiologically acitve agent in pharmaceutical compositons adapted for filling into capsules having an improved rate of release of said physiologically active agent.

An alkali metal carboxymethyl starch, in which sodium is the alkali metal, is represented by the following formula:



and is prepared by reacting starch with chloroacetic acid in the presence of sodium hydroxide.

Other alkali metal derivatives, such as lithium and potassium can be prepared by substituting the appropriate alkali metal hydroxide for the sodium hydroxide and the scope of this invention encompasses such other alkali metal derivatives of carboxymethyl starch.

The alkali metal carboxymethyl starch useful in the novel process of this invention has from about 15 to about 35 carboxymethyl groups, preferably about 25 per 100 glucose units. This means that the degree of substitution (DS) ranges from about 0.15 to 0.35, preferably being about 0.25, which indicates that in general one of the three hydroxyl groups in every fourth glucose unit has been substituted with an alkali metal carboxymethyl moiety. It will be recognized by the skilled starch chemist that there may be some glucose units whereon 2 or possibly all 3 of the hydroxyl groups have been substituted. Nevertheless, the alkali metal carboxymethyl starch useful in the instant invention will have approximately 15 to 35 carboxymethyl groups per 100 glucose units substituted on a hydroxyl moiety.

The amount of the alkali metal carboxymethyl starch needed to provide the improved rate of release of a pharmaceutically active agent from a capsule can vary within wide limits, and it appears that the quantity required may be inversely proportional to the solubility of such active agent. Thus, based on the weight of such active agent present in the capsule, up to about 65 percent by weight of said carboxymethyl starch may be needed to obtain improved release rates of poorly soluble active agents, while an amount as low as 2 by weight may be adequate to produce the desired effect on a highly soluble drug. For most physiologically active agents, however, a range of from about 8 to about 55 percent by weight of the alkali metal carboxymethyl starch is adequate.

The preferred alkali metal carboxymethyl starch for use in the present invention is a sodium carboxymethyl starch which, most advantageously, has a degree of substitution of about 25 carboxymethyl groups per 100 glucose units.

According to a further aspect of the present invention, there is provided a pharmaceutical composition in capsule form having an improved rate of release characterised in that such composition contains from about 2 to about 65 precent by weight, based on the weight of the physiologically active agent present in the composition, of an alkali metal, preferably sodium, carboxymethyl starch having a degree of substitution of from 15 to 35, preferably about 25, carboxymethyl groups per 100 glucose units. The composition may contain the active agent and carboxymethyl starch as the only ingredients or, if desired, other diluents may also be included such as those commonly used in conventional capsule formulations, for example lactose, dextrose, sucrose, sorbitol, mannitol, starch, sodium bicarbonate, methyl cellulose, sodium lauryl sulphate, polyoxyethylene sorbitan monolaurate and methyl and propyl hydroxybenzoates.

The physiologically active agent used in the compositions of the present invention does not appear to be critical to the operation of the invention, although, since the effect of the use of an alkali metal carboxymethyl starch is most noticeable with poorly soluble active agents the latter are likely to be the most commonly used active agents.

The following non-limiting examples will illustrate the types of physiologically active agents to which the method of the present invention may be applied or which may be used in the pharmaceutical compositions of the present invention: cardiovascular drugs such as bethanidine sulphate, methyldopa, penta-erythritol tetranitrate, cyclandelate, phenoxybenzamine hydrochloride, glyceryl trinitrate, ergotamine tartrate, diphenhydramine hydrochloride and dichloralphenazone; central nervous system drugs such as amylobarbital, aspirin, dextropropoxyphene hydrochloride, phenacetin, caffeine, pentazocine hydrochloride, indomethacin, paracetamol, codeine phosphate, mefenamic acid, flufenamic acid, potassium p-aminobenzoate, pentobarbital sodium, ethchlorvinol, carbromal, propiomazine, methaqualone, diphenhydramine, heptabarbital, nitrazepam, quinalbarbital sodium, chlorpromazine, trifluoperazine, nortriptyline, hydroxyzine pamoate, chlordiazepoxide, ethinamate, amitriptyline, medazepam, methylpentynol carbamate, haloperidol, doxepin hydrochloride, prothipendyl hydrochloride, phensuximide, ethosuximide, pyrrobutamine, thenylpyramine, cyclopentamine, mebanazine, chlomipramine, dexamphetamine and imipramine hydrochloride; antibiotics such as tetracycline, novobiocin, chlortetracycline, oxytetracycline, phenthicillin, cephalexin, chloramphenicol, phenoxymethyl penicillin, clindamycin, oleandomycin, flucloxacillin, fusidic acid, paromomycin, erythromycin estolate, propionyl erythromycin, kanamycin sulphate, demethylchlortetracycline, lincomycin, nystatin, cloxacillin, ampicillin, doxycycline; as well as various other drugs such as clofibrate, D(−)penicillamine, nalidixic acid, acetohexamide, methylthiouracil, ephedrine sulphate, chlorprenaline, crotethamide and theophylline.

The present invention is effected by commingling the desired physiologically active agent with the alkali metal carboxymethyl starch to provide a uniform blend. Any of the conventional blending equipment, such as ribbon mixers, paddle mixers, tumbling cones, twin shell blenders, verticle mixers, and the like can be employed to accomplish the commingling. Other appropriate diluents, internal lucricants, preservatives, excipients, and the like can be added to the blender concurrently with said active agent and said carboxymethyl starch so that one operative blending step can be utilized, if desired, to accomplish the obejcts of this invention. The resulting pharmaceutical composition is filled into the appropriate size capsule by conventional filling means to provide unit dose capsules having improved release rates of the physiologically active agent contained therein.

The present invention is further illustrated by the following examples.

EXAMPLE 1

In the following experiment, various physiologically active agents were commingled with 0, 10 and 50 percent by weight, respectively, based on the weight of said active agent, of sodium carboxymethyl starch (SCMS) containing approximately 25 carboxymethyl groups per 100 glucose units. The resulting pharmaceutical compositions were filled into two-piece hard gelatin capsules. The capsules were suspended in a dissolving medium (N/10 hydrochloric acid) at 37°C., and the time in minutes determined for 50 percent of the drug content to enter solution (T_{50}). The results were as follows:

Drug	Drug Solubility	T_{50} SCMS 0%	T_{50} SCMS 10%	T_{50} SCMS 50%
Cephalexin	>120 mg./ml.	16 min.	7.4 min.	2.8 min.
Paracetamol	52 mg./ml.	42 min.	27 min.	21 min.
Aspirin	3.3 mg./ml.	>100 min.	29 min.	2.1 min.
Phenobarbitone	1.65 mg./ml.	>100 min.	>100 min.	3.4 min.
Dextropropoxyphene napsylate	0.78 mg./ml.	>100 min.	>100 min.	48 min.
Amylobarbitone	0.56 mg./ml.	>100 min.	>100 min.	7.4 min.

It is indicated from the above results that, in all cases, an improved release time was achieved from the capsules containing SCMS, but that with poorly soluble physiologically active agents a higher percentage of SCMS was required. Pharmaceutical compositions, adapted for filling into capsules, comprised of a physiologically active agent commingled with an alkali metal carboxymethyl starch are superior to such compositions containing no alkali metal carboxymethyl starch in that the release rate of such active agent from a capsule is substantially and significantly faster.

EXAMPLE 2

In this example, various drugs were mixed with a diluent (starch/lactose in a ratio of 1:1 and a lubricant (magnesium stearate). To the resultant formulations was added 0, 10 or 50 percent by weight, based on the weight of the drug, of SCMS. The finished formulations were filled into hard gelatin capsules so as to give capsules containing the following quantities of ingredients:

Drug	Nominal mg. per Capsule: Active	SCMS	Diluent	Lubricant	Formulation Reference
Ethinamate	500	0	300	8	1
	400	40	200	7	2
	460	230	46	8	3
Phenylbutazone	100	0	150	2.5	4
	100	10	140	2.5	5
	100	50	100	2.5	6
Penicillamine HCl	250	0	150	4	7
	250	25	125	4	8
	250	125	25	4	9

-Continued

Drug	Nominal mg. per Capsule				Formulation Reference
	Active	SCMS	Diluent	Lubricant	
	250	0	150	4	10
Sulphadimidine	250	25	125	4	11
	250	125	25	4	12
	250	0	150	4	13
Acetohexamide	250	25	125	4	14
	250	125	25	4	15
	380	0	228	6	16
Paracetamol	380	38	190	6	17
	380	190	38	6	18

Each of formulations 1 to 18 was divided into three groups. In respect of one group, the T_{50} (as defined above) was immediately measured whilst, in respect of the other two groups, the T_{50} was determined after storage of the capsules at 50°C. for 14 and 28 days respectively. The following results were obtained:

Formulation Reference	T_{50}		
	Initial	14 days at 50°C.	28 days at 50°C.
1	50.9 min.	>60 min.	>60 min.
2	8.6 min.	7.2 min.	8.3 min.
3	5.8 min.	8.5 min.	7.3 min.
4	26.2 min.	>60 min.	>60 min.
5	24.7 min.	32.2 min.	18.8 min.
6	17.9 min.	20.0 min.	21.2 min.
7	5.9 min.	6.1 min.	6.9 min.
8	5.9 min.	5.3 min.	4.9 min.
9	6.4 min.	4.0 min.	3.9 min.
10	9.0 min.	20.2 min.	22.2 min.
11	8.4 min.	8.0 min.	9.7 min.
12	5.2 min.	4.9 min.	3.6 min.
13	>60 min.	49 min.	>60 min.
14	31.5 min.	30.5 min.	29.0 min.
15	18.6 min.	22.5 min.	19.3 min.
16	7.3 min.	17.9 min.	37.9 min.
17	7.6 min.	4.0 min.	9.2 min.
18	2.1 min.	3.0 min.	3.8 min.

From the above tests it will be noted that capsules containing SCMS can be stored at elevated temperatures for long periods of time without encountering any substantial retardation in the rate of release of drugs therefrom, which retardation, as can also be seen from the above results, frequently occurs with conventional encapsulated drug formulations. Indeed, in all instances, the above tests show an improvement in the rate of release of drug after storage for 14 or 28 days when from 10 to 50 percent SCMS is incorporated into the capsules. In most cases, a marked improvement in the T_{50} is also seen in newly formulated capsules containing SCMS.

Since storage of drugs for short periods of 14 or 28 days at 50°C. is recognised in the art as giving results equivalent to those that are obtained when the drugs are stored in room temperature for the usual periods encountered between manufacture and use of the drugs, it will be appreciated from the above results that the incorporation of an alkali metal carboxymethyl starch (of the type hereinbefore defined) into an encapsulated drug formulation provides a most useful means of improving the rate of release of the drug from the capsule.

What is claimed is:

1. A pharmaceutical two-piece hard gelatin capsule comprising a physiologically active agent commingled with an amount, of from about 2 to about 65 percent by weight of the physiologically active agent, as a release rate improving quantity of an alkali metal carboxymethyl starch.

2. The pharmaceutical two-piece hard gelatin capsule of claim **1**, wherein the alkali metal carboxymethyl starch contains from 15 to 35 carboxymethyl groups per 100 glucose units.

3. The pharmaceutical two-piece hard gelatin capsule of claim **1**, wherein the alkali metal is sodium.

4. The pharmaceutical two-piece hard gelatin capsule of claim **1**, wherein sodium is the alkali metal carboxymethyl starch and is present in an amount of from about 2 to about 65 percent by weight of the physiologically active agent.

5. The capsule of claim **1**, wherein said physiologically active agent is ethinamate.

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