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Effect of Some Channeling Agents on the Release of DFK from a Hydrophobic Polymer Matrix

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ABSTRACT

Ethylcellulose, a hydrophobic polymer, when employed at a relatively high concentration in a formulation, especially in sustained release formulation is capable of retarding drug release unless a channeling agent is incorporated. The present study was undertaken to investigate the effect some channeling agents (maize starch, alginic acid, sodium lauryl sulphate (SLS) and polyethylene glycol 4000 (PEG 4000) will have on the release of a poorly water soluble drug, diclofenac potassium (DP) from ethylcellulose matrix. Diclofenac potassium granules and matrix tablets were prepared by the wet granulation method and the tablet properties evaluated as a function of polymer additive include: hardness, friability and dissolution profiles in phosphate buffer (pH 7.5). Results obtained indicated variability in DP release in the presence of the polymer additives. Whereas the presence of maize starch or alginic acid led to an increased release of DP, the presence of SLS or PEG 4000 caused significant retardation in the DP release. The behaviour of SLS and PEG 4000 is consistent with established inconsistencies of their behaviour in formulation, a behaviour which has been attributed to micelle formation when used at certain concentrations in formulations. The release of DP generally changed from anomalous (non-Fickian) to Fickian in the presence of all the additives. The overall results indicated that maize starch or alginic acid can be utilized as channeling agents to enhance the release of DP from ethylcellulose matrix while still maintaining the sustained release integrity of the matrix.

Keywords: Diclofenac potassium, ethylcellulose matrix, channeling agents, enhancement, retardation micelles.

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INTRODUCTION

There has been a significant advance in controlled release technology within the last two decades. This technology has led to the formulation of drugs with desirable release profile in terms of clinical efficacy and improved patients compliance. Sustained release of drugs is commonly achieved by encapsulating the drug in a hydrophilic or hydrophobic polymer matrix or a combination of both. While hydrophilic polymers provide a more desirable drug release profile, cost effectiveness and regulatory acceptance [1], hydrophobic polymers on the other hand provide good advantages ranging from good stability at varying pH and moisture levels, to well established safe applications. Hydrophobic polymers such as ethylcellulose, is suitable as a sustained release matrix for highly soluble drugs. When it is employed as a matrix for a hydrophobic drug, inclusion of a channeling agent is required [2]. Channeling agents are hydrophilic polymers which create interstitial spaces within the tablet matrix thereby permitting fluid movement in and out of the tablet matrix. By such action, incorporated drug is solubilised in the imbibed fuid leading to increased drug release process. Maize starch and alginic acid have been used in this regard [3,4].

In the present work, the comparative performance of four polymers (maize starch, alginic acid, SLS and PEG 4000) as channeling agents in ethylcellulose matrix based sustained release tablet formulation of Diclofenac potassium was investigated.

MATERIALS AND METHODS

EXPERIMENTAL

Materials

Maize starch (May & Baker, England), alginic acid, sodium laurylsulphate, polyethylene glycol 4000 (Sigma chem.co, USA), diclofenac potassium is a general gift from SyCom Pharmaceutical India. All other reagents are of Analar grade.

Method

Preparation of Diclofenac potassium (DP) sustained release Tablets.

Five batches of DP sustained release tablets were prepared according to the composition presented in the Table 1.

Diclofenac potassium powder, Cellocarp and either of the polymers (maize starch, alginic acid, SLS and PEG 4000) were mixed and titurated in a mortar to a homogenous mixture. Weighed quantity of ethylcellulose was dispersed in 95% ethanol (15 mL) and titurated to a homogenous wet mass and the wet mass was screened through a 1.70 mm stainless steel sieve. Screened granules were dried in an oven at 40^{o}C for 24 h, rescreened through 1.70 mm

stainless steel sieve, and stored in well closed specimen amber coloured bottles. A batch that contained none of the polymer additive was similarly prepared.

Table 1: Formular for preparing Diclofenac Potassium tablets

INGREDIENTS	BATCHES				
	DP1	DP2	DP3	DP3	DP4
Diclofenac potassium Powder (mg)	50.0	50.0	50.0	50.0	50.0
Ethylcellulose in Ethanol (%)	25.0	25.0	25.0	25.0	25.0
Maize starch (%)	-	10.0	-	-	-
Alginic acid (%)	-	-	10.0	-	-
Sodium lauryl sulphate (%)	-	-	-	10.0	-
Polyethylene glycol (%)	-	-	-	-	10.0
Magnessium stearate (% $^{w}/_{w}$)	1.0	1.0	1.0	1.0	1.0
Cellocarp (mg) q.s to 400mg					

Compression of Tablets

Prior to compression, all five granule batches were lubricated with 1% magnessium stearate. Lubricated granules were compressed into tablets with a BMI Manesty single Punch Tabletting machine fitted with 9.5mm flat faced punches. Compression pressure was maintained at 282.5 mPa and hundred tablets were produced for each batch. Tablet weights ranged from 360 to 390 mg. Prepared tablets were evaluated for hardness, friability and assay of active ingredients using standard methods [5].

Dissolution Profile studies

The Erweka DT dissolution apparatus fitted with a paddle that was operated at 50 rpm was used. The dissolution medium consisted of freshly prepared phosphate buffer (pH 7.5) maintained at 37± 1^{o}C. A tablet from each batch was placed in a basket (mesh size 325 mm) immersed half way into the dissolution medium. Volumes (10 mL) were withdrawn at predetermined time intervals and analyzed spectrophometrically at 275 nm. Values plotted are a mean of two replicate determinations.

RESULTS AND DISCUSSION

The presence of the additives caused a marked reduction in the hardness and the friability of the tablets (Table 2). The batch (DP1) that contained no additive was highly friable with friability values as high as 61.68%. Those containing SLS or PEG 4000 were non-friable, while the batch containing maize starch had friability values of 2.7%. The assay results of the batches ranged from 97.90 to 100.83% (Table 2). A graphical representation of the cummulative percent of DP released over 6 h is shown in figure 1.

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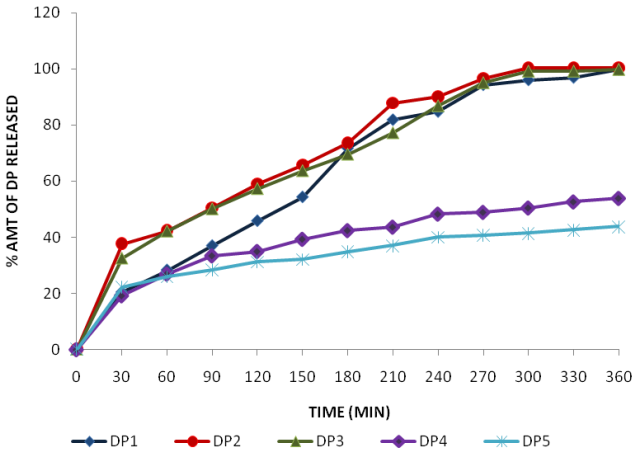

Fig. 1: Release profiles of DP from ethylcellulose matrix

Table 2: Some Properties of DP Sustained Release Tablets

Polymer Additive	Parameters		
	Hardness (KgF)	Friability (%)	Assay (%)
Maize starch	5.5 ± 0.81	0.80	97.90
Alginic acid	3.5 ± 0.40	2.70	99.33
SLS	5.5 ± 0.45	0.00	100.42
PEG 4000	4.6 ± 0.29	0.00	100.83
Control	7.0 ± 0.00	61.68	97.96

Table 3: Release exponent of DP from Ethylcellulose matrix

Release Exponent (n)	Polymer Additive				
	Maize starch	Alginic acid	SLS	PEG 4000	Control
	0.46	0.49	0.57	0.52	0.71

The polymer additives exerted varying effects on DP release from the tablets. Maize starch and alginic acid exerted an enhancement effect on the DP release while SLS and PEG 4000 exerted a retardant effect on DP release. Polymers such as Alginic acid, PEG 4000, Primogel and Maize starch may enhance the release of drugs from polymer matrices by acting as channeling agents, modification of the matrix barrier properties or by disintegration inducement [6-9]. The presence of maize starch and carboxymethyl starch (Primogel^{R}) were found to enhance the release of frusemide from a fatty polymer matrix and from hydrogenated vegetable lubricant respectively [3,6]. Sodium lauryl sulphate and PEG 4000 on the other hand have been reported to exert variable effects on drug release when incorporated into formulations[10-13]. Reports concerning the usefulness of surfactants such as SLS and PEG 4000 in enhancing gastro-intestinal (GIT) absorption of drugs have been conflicting [12]. Enhancement as well as inhibition of the GIT absorption and pharmacological activity of drugs has been observed when surfactants were added to drug formulations.When the effect of incorporated surfactants in a formulation results in retardation of drug release, a special type of complexation reaction between the drug and surfactant may have taken place leading to

aggregation of the surfactant molecules (micelles) [12]. Surfactant exert a two phase effect, which is concentration dependent. Below the critical micelle concentration (CMC), release / absorption of drugs may be enhanced due to a better contact of drug with the dissolution medium *in vitro* or absorbing membrane *in vivo*. It has been observed that above the CMC, a portion of the drug molecules may become entrapped in micelles and as such, unavailable for absorption *in vivo* or release *in vitro*. The release / absorption retarding effect usually predominate at higher surfactant concentrations because a larger fraction of the drug is bound to micelles [13]. The phenomenon of micellization at relatively high concentrations (10%) is considered responsible for the retarding effect of SLS and PEG 4000 on DP release from ethylcellulose matrix. The release of DP generally changed from anomalous (non-fickian) to Fickian [14] in the presence of all the four additives (Table 3).

CONCLUSION

The overall results indicated the usefulness of maize starch and alginic acid as channeling agents for DP embedded in ethylcellulose matrix. Sodium lauryl sulphate and PEG 4000 may not be recommended as a channeling agents in DP sustained release formulations especially at a relatively high concentrations (up to 10%).

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