Development and Evaluation of Ethylcellulose Coated Controlled Release Pellets

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Pellets of isosorbide-5-mononitrate (ISMN) and carbamazepine (CBZ), were prepared by suspension layering and powder layering techniques, respectively. The different processing conditions were optimized. The drug loaded pellets were coated using ethylcellulose as release retardant. Different coat weights were applied and pellets were subjected to *in vitro* release studies. Formulations showing similar *in vitro* release profile to the innovator's product under different conditions of pH and agitation were selected for accelerated stability studies. These were found to be stable under different conditions of storage, for a period of 6 months.

Controlled release pellets offer significant advantages over single unit dosage forms of drugs[1]. Besides maximizing drug absorption and reducing peak plasma fluctuations and inter-subject variability, they even minimize the chances of dose dumping[2]. Further, these pellets provide low surface area to volume ratio and therefore an ideal shape for film coatings. Ethyl cellulose is commonly used to impart controlled release film coatings to oral dosage forms[3].

Isosorbide-5-mononitrate (ISMN) is a well-known nitro vasodilator used in prophylactic treatment of angina pectoris and myocardial ischaemia. The development of tolerance to ISMN is a potential clinical problem on long term therapy[4]. Carbamazepine (CBZ) is a first line drug used in the treatment of most forms of epilepsies and trigeminal neuralgia. It has a narrow therapeutic window (4-12 μg/ml) and diurnal variations in plasma concentration of CBZ due to autoinduction lead to several side effects[5]. Controlled release preparation of these drugs is necessary to improve compliance and decrease side effects associated with conventional dosage forms of these drugs.

In this study, we investigated the use of ethylcellulose as a release retarding polymer, to prepare controlled release pellets of both, a water soluble drug, ISMN and a water insoluble drug, CBZ.

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Isosorbide-5-mononitrate (80% triturate, Natco Pharma), carbamazepine IP/BP/USP (Umedica Labs), non pareil seeds (NPS), eudragit RL and RS, ethyl cellulose (EC) 20 cps and povidone K-30 (PVP) were used. Other chemicals and solvents used include, isopropanol (IPA), dichloromethane (DCM) and dibutyl phthalate (DBP) which, were of analytical reagent grade. The tablets Elantan Long were obtained from Schwarz Pharma, Monheim and Tegretol Retard (Ciba-Geigy, U.K.) was obtained from International market. The preparation of controlled release pellets of ISMN and CBZ involved the following steps:

A. Loading of nonpareil seeds with drug

B. Coating of pellets with a release retardant

The processing conditions for the drug-loading in a dish pelletizer and coating with EC in a conventional coating pan, were optimized. The loading of each drug on the NPS (#24/30) was carried out in a stainless steel dish pelletizer (16" diameter) attached to a Kalweka Machine HD 410E (M/s Karnavati Eng., Kadi). A pilot type 64M spray gun was used to spray the binding solution.

ISMN pellets were prepared by *suspension layering* technique. Firstly, a drug suspension was prepared by adding 31.25 g of 80% of ISMN to 200 ml of IPA. To this, 3 g of Eudragit RS 100 was added as binder and the mixture was stirred for 1 h. One hundred grams of NPS

TABLE 1 : PHYSICAL CHARACTERISTICS OF ISMN AND CBZ PELLETS

Parameter	ISMN Pellets	CBZ Pellets	
		IR	CR
Bulk Density (g/cc)	0.77	0.57	0.54
Sieve Analysis			
22 mesh	6.0%	7.6%	8.8%
18/22 mesh	72.0%	2.3%	4.7%
16/18 mesh	16.0%	1.0%	2.5%
14/16 mesh	3.0%	88.0%	81.4%
14 mesh	3.0%	3.1%	2.4%
l/b ratio	0.95	0.92	0.92

IR - Immediate release portion; CR - Controlled release portion

were loaded in a dish pelletizer and the drug suspension was sprayed onto the revolving bed of NPS.

CBZ pellets were prepared by *powder layering* technique. Two types of pellets were prepared, immediate release pellets (IR) by loading 60 g of drug on 30 g of NPS using 5% w/v PVP in IPA and controlled release pellets (CR) by loading 160 g of drug on 80 g of NPS using 3% Eudragit RL 100 in IPA. After loading of drugs, both ISMN and CBZ pellets were dried for 4 h at 40° in a conventional tray drier.

The coating on the drug loaded pellets of ISMN and CBZ was carried out using the following process : A # 22/24 fraction of ISMN pellets were chosen for the purpose. A coating suspension of 1% EC in IPA:DCM (60:40 v/v) containing 0.2% w/v of DBP and erythrosine (lake) was prepared and sprayed on the drug loaded pellets using a pilot type 64M spray gun in a conventional coating pan. For coating of CBZ (CR) pellets #16/18 fraction of pellets was selected. A coating suspension of 2% EC in IPA:DCM (60:40 v/v) containing 0.1% w/v DBP and Sunset yellow (lake) colour, was sprayed on the drug loaded pellets, in a similar way, as for ISMN pellets. In both cases, a one minute on and one minute off spray cycle was maintained throughout the coating process. At different time intervals, samples of EC coated pellets were withdrawn and *in vitro* studies were performed to determine the effect of different coat weights of EC on the *in vitro* release of the drugs.

USP2 (Paddle) dissolution apparatus (Electrolab) was used for *in vitro* studies. 900 ml distilled water at 37±1° was used as the dissolution medium in both cases. For CBZ release, studies were conducted in presence of 1% SLS in the dissolution medium. 10 ml of samples were withdrawn at 0.5, 1, 2, 3, 4, 5 and 8 h, filtered and analysed by HPLC at 220 nm and UV at 285 nm in case of ISMN and CBZ respectively. Formulations having similar *in vitro* release pattern were studied at different pH levels, (1.2, 4.5 and 7.2) and agitation speeds (25, 75 and 100 rpm). In case of CBZ, dissolution was carried out at these pH levels in presence of 1% SLS. Formulations having similar *in vitro* release profile to the innovator's product were selected for stability studies.

The pellets of the selected formulation were evaluated for bulk density, sieve analysis, assay (Drug content), content uniformity, l/b ratio and *in vitro* dissolution. The selected formulation of ISMN and CBZ equivalent to 50 mg and 200 mg dose respectively, were filled in 0 size semi-transparent capsules and blister packed using PVDC lined polyethylene blisters. They were then subjected to stability studies at 25±0.5°, ambient, 37±1° and 75% RH and 45±1° conditions. During stability studies, they were assessed for drug content by stability indicating HPLC method and *in vitro* dissolution.

The optimized processing conditions for drug loading and coating of pellets included the angle and speed of dish pelletizer/coating pan to be 35° and 35 rpm

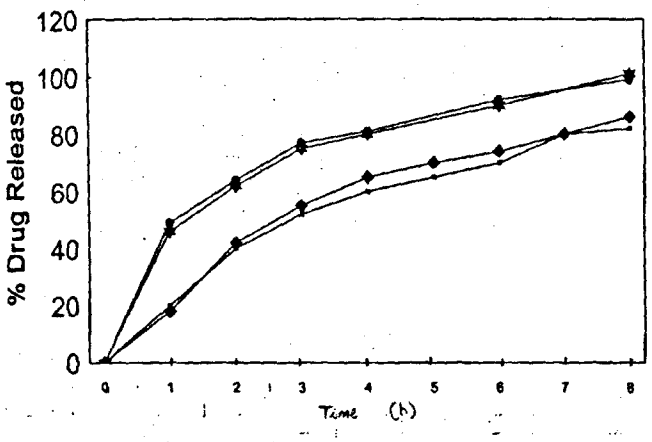

Fig. 1 : Comparative *in vitro* release profiles

***In vitro* profiles of developed ISMN formulation (-◆-) and CBZ formulation (-★-) in comparison with reference ISMN (-■-) and CBZ (-●-) formulations**

respectively. The spray rate was optimized as 2-3 ml/ min. and spray pressure was kept between 2-2.2 kg/cm^2. *In vitro* release studies showed that the uncoated pellets in both cases released the drug completely in 1 h. In both cases, the per cent drug released was found to decrease with increasing coat weights. The release followed first order and zero order in case of ISMN and CBZ respectively. In case of CBZ pellets, a suitable proportion of CBZ-IR were mixed with CBZ-CR pellets, to achieve the required *in vitro* release pattern.

The results of the physical characterization of the selected formulation of both ISMN and CBZ pellets, is shown in Table 1. The maximum yield for pellets, in case of ISMN and CBZ was for 18/22 and 14/16 mesh size respectively. The average drug content obtained from ISMN and CBZ capsules was 97.36% and 98.63% respectively. Content uniformity values for 6 capsules ranged from 97.6-98.4% for ISMN and 98-99.4% for CBZ. The comparative release profile of the selected formulations along with the respective innovator's product are shown in Figure 1. The release profiles are comparable in both cases. The *in vitro* release matched innovator's product at different pH and agitation rates also.

The average drug content and *in vitro* release remained the same for ISMN and CBZ at different conditions of temperature and humidity, for a period 6 months, suggesting that both the formulations are stable at the required conditions of storage. In conclusion, ethyl cellulose could be used as a release retarding polymer to prepare stable controlled release pellets with similar *in vitro* release profile as that of innovator's, for both ISMN and CBZ.

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REFERENCES

1. Bechgard, H. and Nielson, G.H., **Drug Dev. Ind. Pharm.** 1978, 4, 53.
2. Zimm, K.R., Schwartz, J.B., **Pharm. Dev.Technol.**, 1996, 1, 37.
3. Porter, S.C., **Drug. Dev. Ind. Pharm.**, 1989, 15, 1459.
4. Mohammed, S.E., Susan H., Backer M., **Pharm. J.**, 1994, 252, 129.
5. Larkin, J.G. and Melellan, A., **Br. J. Clin. Pharm.**, 1989, 27, 313.