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Effect of plasticizer on drug crystallinity of hydroxypropyl methylcellulose matrix film

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ABSTRACT

Effect of different hydrophilic plasticizers on drug crystallinity of hydroxypropyl methylcellulose (HPMC) matrix film was studied. HPMC films containing telmisartan using different plasticizers were prepared by casting method. Drug crystallinity in the films was examined using polarized light microscopy (PLM), scanning electron microscopy (SEM), and x-ray diffractometry (XRD) to describe their phase behavior/solid state miscibility/crystal growth and drug–polymer–plasticizer interaction. HPMC and plasticizer were compatible with the drug and no phase separation was observed upon solvent evaporation. Plasticized-HPMC contributed a major role in the significant inhibition of crystal growth of the drug in the film. The triethanolamine film produced a relatively smooth surface in comparison to the other films in the submicron level. The films have not shown any significant changes even after exposure to stress (40° C/75% RH, 6 w). Triethanolamine as plasticizer brought about amorphization of telmisartan to the maximum extent in the film which is technologically more advantageous than the others owing to its anticipated better bioavailability.

1. Introduction

Cellulose ethers, the hydrophilic polymers derived from cellulose have been used since long time in pharmaceutical industries. Moreover, they exhibit appropriate biological properties which make them suitable for biomedical applications [1]. Hydroxypropyl methylcellulose (HPMC), a cellulose derivative polymer, is used in the preparation of many film type drug delivery systems [2,3] and also other biomaterial matrices [4,5]. Plasticizers play a very important role in the formulation of film type drug delivery systems. Without a plasticizer, a very hard and brittle type film is produced. Plasticizers used in the film formulation are selected mainly according to the biocompatibility, plasticizer–polymer–drug compatibility, drug release and flexibility [6–9]. The workability and flexibility of the polymer are improved by increasing the intermolecular separation of the polymer molecules after loosening of tightness of intermolecular forces upon incorporation of plasticizer [10–14] and this results in an improvement of patient compliance. The lubrication theory describes that plasticizers act as internal lubricants by reducing frictional forces between polymer chains. As per gel theory plasticizers play role in breaking polymer–polymer interactions (e.g., hydrogen bonds and van der Waals or ionic forces). The aggregation process caused by the intermolecular attraction of the polymer is reduced after the incorporation of the plasticizer and it can also cause in an increase in bioadhesiveness. Gal and Nussinovitch [15] have reported that inclusion of plasticizer in the transdermal patches exhibited an additional skin bioadhesion. Polyethylene glycols and triethanolamine showed high plasticizing effect [16]. Lin et al. [6,17] have examined that addition of polyethylene glycol 200 or propylene glycol as a secondary plasticizer improved flexibility, adhesive properties and transparency of the film. Polyethylene glycols are highly biocompatible and their miscibility decreases with molecular mass [18]. PEG very effectively plasticized in a 30% concentration of poly(lactic acid) but above 50% it caused an increasing crystallinity of PEG, resulting in an increase in modulus and a corresponding decrease in elongation at break [19]. PEG 400 was proved to be a more effective plasticizer [20] than PEG1000 for HPMC films [21–23]. Dimethyl sulfoxide (low toxic potential) is included in the selection list of plasticizers also appropriate for dosage forms in the 35th edition of the United States Pharmacopoeia.

In the present study, HPMC films plasticized with propylene glycol (PG), polyethylene glycol 400 (PEG), dimethyl sulfoxide (DMSO) or triethanolamine (TEA) were produced incorporating a model antihypertensive drug, telmisartan. How the crystallinity of telmisartan in the HPMC matrix has been influenced by the plasticizer was

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Table 1
Formulation of hydroxypropyl methylcellulose films containing telmisartan, plasticized with different hydrophilic plasticizers.

Formulation	Telmisartan: HPMC K15	Plasticizer used	Plasticizer[a] (%)	Casting solvent
Tpg_{10}	1:3	PG	10	Water and ethanol
Tpg_{30}	1:3	PG	30	Water and ethanol
$Tpeg_{30}$	1:3	PEG	30	Water and ethanol
$Tdmso_{30}$	1:3	DMSO	30	Water and ethanol
$Ttea_{30}$	1:3	TEA	30	Water and ethanol

[a] Plasticizer as percentage of polymer weight.

the objective of the study. Extensive literature survey revealed that this type of study has not been performed earlier. All plasticizers chosen were hydrophilic substances containing hydroxyl or amino functions. The prepared films were analyzed using scanning electron microscopy (SEM), polarized light microscopy (PLM), and x-ray diffractometry (XRD) to describe their phase behavior/solid state miscibility/crystal growth and drug–polymer–plasticizer interaction. Moreover, physical stability of the films was performed by analyzing after exposure at 40° C/75% RH for 6 weeks. A mechanistic explanation on the evolution of unique physical structures in the films prepared from a variety of plasticizers was postulated based on the observed results.

2. Experimental

2.1. Fabrication of films

Matrix films of hydroxypropyl methylcellulose K15M (Biodeals Pharma Ltd, India) as hydrophilic polymer containing telmisartan were prepared by casting and solvent evaporation technique [24,25] using different plasticizers such as propylene glycol, polyethylene glycol 400, triethanolamine (all of Merck, Mumbai, India) and dimethyl sulfoxide (Burgoyne, Mumbai, India)). HPMC was soaked in cold distilled water and left overnight for complete swelling. Separately, telmisartan (Biodeals Pharma Ltd, India) was dissolved in ethanol (same volume as of water used in HPMC soaking) followed by the addition of plasticizer with continuous stirring (Magnetic stirrer, REMI 1MLH, India). Drug solution was poured on the swelled polymer and a uniform dispersion was prepared with constant magnetic stirring for 12 h. Casting of the final dispersion was then done in a flat bottomed petridish and dried at 40° C for 48 h or more for complete drying. The dried films were preserved in an air tight container in a cool dark place until use. The composition of the polymeric films has been tabulated in Table 1.

2.2. Evaluation of physical characteristics of the films

Individually prepared films were accurately weighed and placed in a desiccator containing activated silica at laboratory ambient temperature until two successive weights found constant. Percent moisture content was evaluated as a difference between initial and final weight with respect to final weight [8]. The thickness of the films was measured at six different places of each formulated film using digital micrometer (Mitutoyo, Japan). Folding endurance was determined by repeatedly folding a strip of film at the same place until it broke or 200 times which is considered satisfactory to reveal good film properties [26]. For determination of surface pH of each film Bottenberg et al. method was adopted [27]. A small strip of each film was allowed to swell by keeping it in contact with 1 ml of distilled water (pH 6.5 ± 0.5) for 2 h at laboratory ambient temperature, and the pH was recorded by bringing the electrode into contact with the surface of the film and allowing it to equilibrate for 1 min. A mean of four readings was noted for each formulation. For moisture uptake determination accurately weighed films kept in desiccators at ambient temperature for 24 h were taken out and placed in desiccator containing 100 ml of supersaturated solution of potassium chloride, sodium chloride and aluminium chloride to maintain 84%,74% and 79% relative humidity respectively until a constant weight for the film was obtained. The percentage of moisture uptake was calculated as the difference between final and initial weight with respect to initial weight and a mean of four determinations was recorded for each film.

2.3. Polarized light microscopy

Polarized light microscopy was performed with an Olympus MLX polarizing optical microscope. Samples of telmisartan pure drug crystals and films were spread over a glass slide and covered with another slide. The specimens were visualized for the presence of birefringence under polarized light and pictured using a digital camera (Olympus Imaging Corp, Model: E-520, Software: Version 1.1). All images were taken at room temperature with an exposure time of 0.2 s.

2.4. Scanning electron microscopy

The surface morphology of the films was visualized by a Scanning electron microscope (JSM- 6390, JEOL, Tokyo, Japan). The dried samples were sputtered with gold and scanned at room temperature using an accelerated voltage of 5/15 kV.

2.5. X-ray diffractometry

The x-ray diffraction patterns of pure telmisartan (as available) and the films were recorded using x-ray diffractometer (Model: Philips analytical X-Ray with PC-APD, Diffraction Software). The voltage and current were 40 kv and 15 mA, respectively. Anode Material Cu, K-Alpha (radiation 1.5406 Å) was used as a source of x-rays. Measurements were undertaken at a scan speed of 1○/min for the scanning angle ranging from 10° to 70°.

2.6. Differential scanning calorimetry

Pure telmisartan and films were subjected to thermal analysis by differential scanning calorimetry (DSC Q10 V9.4 Build 287) to examine possible interactions between drug and excipients. Samples were weighed into the DSC pan, and the sealed pan was placed in the sample side of the instrument. Scans were carried out at a rate of 10 °C/min at temperatures of between 30 °C and 330 °C, using a nitrogen gas purge at 50 ml/min.

2.7. In-vitro dissolution

USP XXIV dissolution apparatus (Electrolab, dissolution tester USP, TDT06L, India) rotating paddle method was used to study drug release from the films. A small strip of each film was accurately weighed and attached to the glass slide with an adhesive (cyanoacrylate) and placed inside bottom of the dissolution vessel. After 2 min, the vessel was filled with 1000 ml of phosphate buffer (pH 7.4) and maintained at 37.0 ± 0.5 °C while stirring at 50 rpm and dissolution continued. At specified intervals of time, samples were withdrawn through 0.45 μ membrane filter and analyzed spectrophotometrically and reported as an average of three measurements.

2.8. Stability of the films

Films were placed in open petridish and exposed at 40 °C/75% RH in a humidity cabinet (Temperature Cum Humidity Controller, Thermotech, TH-7004, Model: IK-116, IKON Instrument, India).