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# SYNTHESIS AND APPLICATION OF METHACRYLATE POLYMERS IN THE FORMULATION OF MATRIX TABLETS

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## *ABSTRACT*

Polymers were prepared by using two types of methacrylate monomers viz. hydrophobic monomers (methymethacrylate, butylmethacrylate) and hydrophilic monomers (2-hydroxy ethyl methacrylate, 2-hydroxy propyl methacrylate) using solution polymerisation method. Characterisation of the physico-chemical properties of the polymers was studied. The polymers were then evaluated as matrix formers for drugs selected on the basis of their aqueous solubility.

## *INTRODUCTION*

Polymeric systems have attracted wide attention in the controlled release of drugs[1]. Of the synthetic polymers, methacrylate polymers are non toxic and biocompatible[2]. Such types of polymers can be easily prepared by solution polymerisation, which involves polymerisation of monomers in the presence of free radical initiators, dissolved in suitable solvent. The present work involved synthesis of methacrylate polymers. All these polymers were purified and analysed prior to use. These were then characterised by physical constants like refractive index, per cent acidity, intrinsic viscosity and water fraction. The

polymers were then utilised as matrix formers for drugs like propranolol hydrochloride (**PH**) and anhydrous theophylline (**TH**), selected on the basis of their aqueous solubility.

## *EXPERIMENTAL*

**Materials**:

2-hydroxyethyl methacrylate (2HEMA) and 2-hydroxypropyl methacrylate (2HPMA) from Fluka, methyl methacrylate (MMA) and butyl methacrylate (BMA) acid from BDH Ltd., propranolol hydrochloride (**PH**) and theophylline (**TH**) (Cipla, Bombay) and solvents.

**Method**:

100 g of each of the purified monomers and 1 g of the free radical initiator, benzoyl peroxide were separately dissolved in dry distilled methanol. The ratio of the total monomer to solvent used was kept constant at 1:3. The solutions were placed in a three necked round bottom flask fitted with a condensor and an overhead mechanical stirrer (300-400 rpm). The assembly was placed in a water bath maintained at 80°C for 4 hrs. Absence of the monomer spot on a TLC chromatoplate indicated completion of the polymerisation reaction. The contents of the flask were then poured in excess of distilled water to precipitate the polymerised product and then soaked overnight to leach out any unwanted monomers. The polymer obtained was washed several times with water to remove any soluble impuriities and traces of residual solvent. Purification was carried out by redissolving the product and reprecipitating in water. The filtered product was dried, powdered and stored in air tight containers.

**Characterisation of Polymers**[3]:

The parameters evaluated to characterise the synthesised polymers were percent acidity, intrinsic viscosity, refractive index (RI), water fraction on equilibrium hydration ($\%W_f$) (TABLE 1) and solubility at different pH values. Representative samples were used for Differential Thermal Analysis (DTA) study (Stanton Red Craft). Alumina was used as the reference and thermograms are shown in FIG. 1.

**Film Permeability Studies**:

The synthesised polymers were dissolved in isopropanol: methylene dichloride (50:50) solvent mixture and triacetin (as plasticizer) was added to it in ratios specified in TABLE-3. Polymer solutions of different compositions were casted on mercury pool. To determine the semipermeability, free film (20-25 um thickness) was placed between the flanges of two compartments A & B (FIG 2). Compartment A was filled with distilled water and compartment B with 2% w/v NaCl containing drug (40 ug/ml). The whole system was stirred for 3 hrs at 300 rpm. At regular intervals, the amount of the drug permeated in compartment A was analysed using Beckmann DB spectro-photometer at 290 nm (for propranolol hydrochloride).

**Formulation of Matrix Tablets**:

The drug and polymer were mixed in specified ratios (TABLE-2) and wet granulated with PVP 4% in ethanol:isopropanol (60:40) solvent mixture. The wet mass was then screened through sieve no. 12 and the resulting granules were dried at 60°C for 1 hr. The 20/40 mesh fraction was collected and lubricated with

***TABLE 1: Characterisation of Polymers***

| Polymers | % Yield | Percent acidity | Intrinsic viscosity | RI | % $W_f$ |
|---|---|---|---|---|---|
| p(HEMA) | 68.2±5.9 | - | 0.57 | 1.35 | 48.54±2.10 |
| p(HPMA) | 71.3±4.2 | - | 0.51 | 1.34 | 53.54±1.12 |
| p(MMA) | 78.5±3.5 | 95.5 | 0.43 | 1.30 | 45.39±1.50 |
| p(BMA) | 76.5±6.3 | 93.2 | 0.42 | 1.28 | 43.25±2.30 |

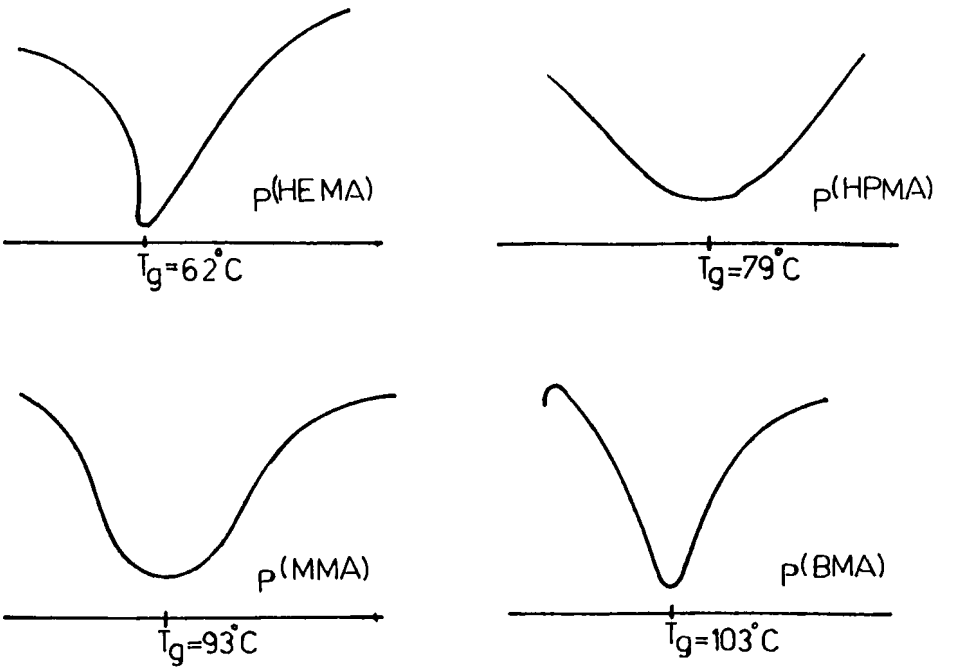


Fig. 1. Differential Thermograms

*TABLE 2: Dissolution Data of Matrices*

| Formulation | Regression coeff. (R) | $K_1$ ($hr^{-1}$) | $T_{50}$ (hr) | $T_{90}$ (hr) | Release index |
|---|---|---|---|---|---|
| **PH:LAC:p(HPMA)** | | | | | |
| 0.8: 1.2: 0.5 | 0.9950 | 0.250 | 1.98 | 8.30 | 0.40 |
| 0.8: 0.7: 1.0 | 0.9928 | 0.190 | 3.14 | 10.60 | 0.47 |
| **PH:LAC:p(HEMA)** | | | | | |
| 0.8: 1.2: 0.5 | 0.9878 | 7.400 | 1.25 | 6.60 | 0.39 |
| 0.8: 0.7: 1.0 | 0.9882 | 0.190 | 2.07 | 10.41 | 0.37 |
| **TH:LAC:p(HPMA)** | | | | | |
| 1.0: 1.25: 0.25 | 0.9873 | 0.278 | 1.49 | 7.37 | 0.36 |
| 1.0: 1.00: 0.50 | 0.9967 | 0.160 | 2.37 | 12.29 | 0.34 |
| 1.0: 0.75: 0.75 | 0.9483 | 0.083 | 5.36 | 24.70 | 0.37 |
| **TH:LAC:p(HEMA)** | | | | | |
| 1.0: 1.25: 0.25 | 0.9873 | 0.230 | 1.69 | 8.69 | 0.35 |
| 1.0: 1.00: 0.50 | 0.9976 | 0.122 | 2.93 | 16.07 | 0.38 |
| 1.0: 0.75: 0.75 | 0.9881 | 0.112 | 5.11 | 19.40 | 0.49 |
| **PH:LAC:p(MMA)** | | | | | |
| 0.8: 1.2: 0.5 | 0.9646 | 0.166 | 4.08 | 13.75 | 0.58 |
| 0.8: 0.7: 1.0 | 0.9975 | 0.119 | 5.04 | 19.55 | 0.54 |
| **PH:LAC:p(BMA)** | | | | | |
| 0.8: 1.2: 0.5 | 0.9943 | 6.810 | 3.90 | 9.80 | 0.49 |
| 0.8: 0.7: 1.0 | 0.99922 | 0.144 | 3.60 | 14.40 | 0.50 |
| **TH:LAC:p(MMA)** | | | | | |
| 1.0: 1.0: 0.5 | 0.9884 | 0.071 | 8.49 | 31.07 | 0.54 |
| 1.0: 0.5: 1.0 | 0.9991 | 0.065 | 10.00 | 34.62 | 0.69 |
| **TH:LAC:p(BMA)** | | | | | |
| 1.0: 1.0: 0.5 | 0.9964 | 4.010 | 11.40 | 21.40 | 0.74 |
| 1.0: 0.5: 1.0 | 0.9968 | 3.900 | 11.70 | 21.88 | 0.72 |
| **PH:DCP:p(HPMA)** | | | | | |
| 0.8: 1.2: 0.5 | 0.9868 | 5.900 | 4.03 | 10.80 | 0.39 |
| **PH:MCC:p(HPMA)** | | | | | |
| 0.8: 1.2: 0.5 | 0.9947 | 5.300 | 3.80 | 11.36 | 0.36 |

***TABLE 3: Semipermeability Studies of Free Films***

| Composition (5%w/v) | | Propranolol release in Comp. A (ug/25 ml) 0.5hr | 1hr | 1.5hr | 2hr | 2.5hr | 3hr |
|---|---|---|---|---|---|---|---|
| **p(HPMA):TR** | 2:7.5 | 68.8 | 78.5 | 82.0 | 88.0 | 87.9 | 96.8 |
| | 2:10 | 68.3 | 72.5 | 78.1 | 79.9 | 82.2 | 84.5 |
| **p(HEMA):TR** | 1:7.5 | 72.5 | 79.8 | 85.6 | 88.8 | 92.5 | 98.9 |
| | 1:10 | 68.5 | 76.3 | 79.8 | 81.5 | 83.5 | 84.2 |
| **p(MMA):TR** | 2:10 | 42.5 | 45.5 | 46.6 | 47.9 | 50.2 | 57.7 |

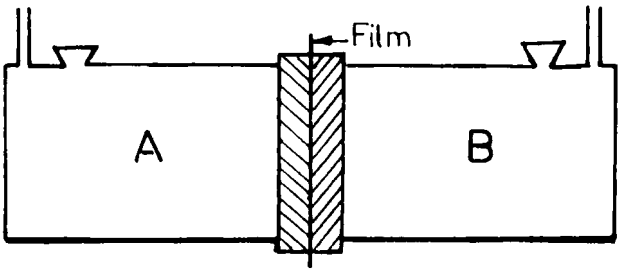


Fig. 2. Permeability Cell

1% talc and 1% magnesium stearate. Various diluents like lactose(LC), dicalcium phosphate (DCP) and microcrystalline cellulose (MCC) were used (TABLE-2). Compression was done using 9.5 mm flat faced die and punch, on a Cadmach single stroke tabletting machine at 4-6 $kg/cm^2$ pressure.

*In vitro* drug dissolution was carried out on USP rotating basket assembly[4] containing 900 ml of pH 7.4 phosphate buffer as the dissolution medium. Aliquots were withdrawn at regular intervals and analysed on Beckmann DB spectro- photometer at $\lambda_{max}$ = 290 nm and 272 nm for propranolol hydrochloride (PH) and theophylline (TH) respectively.

**Stability Studies**:

The matrix tablets were kept at 37°C , 45°C, 60°C and 75%RH for accelerated stability testing and evaluated for physical appearance, drug content and *in vitro* dissolution studies.

## *RESULTS AND DISCUSSIONS*

The solution polymerisation method used for the synthesis of polymers offers several advantages viz. solvent employed dissolves the monomer, initiator and the final polymer and accounts for more efficient heat transfer. Purification of polymers is important to ensure that there are no traces of unreacted monomer or of residual solvent.

All statistical analysis were done using students `t´ test. Increase in the intrinsic viscosity is due to increase in the molecular weight of polymers. The percent water fraction indicates the hydrophilicity of the polymers. Hence hydrophilic polymers formed from water soluble monomers; 2HEMA and 2HPMA showed a higher water retention capacity as compared to the other water insoluble monomers. Percent acidity was determined using titrimetric analysis. The polymers showed good solubility in methylene dichloride, isopropanol, acetone and chloroform. Polymers were however insoluble in the range of pH 1.2 to 6.8 Differential thermograms of p(HEMA), p(HPMA), p(MMA) and p(BMA) showed endotherms at 62°C, 79°C, 93°C and 103°C respectively.

**Matrix Tablets**:

Good flow properties and % compressibilty were exhibited by granules. Fickian and non-Fickian diffusion was characterised by the following equation

$$M_t/M_\infty = kt^n$$

where, $M_t/M_\infty$ is the fraction released at time `t´,
k = characteristic constant, n = release index
n<0.5 = Fickian diffusion, n=1 is Case II transport
0.5<n<1 = Non-Fickian diffusion mechanism

Hydrophobic polymers; p(MMA) and p(MAA) retarded drug release to a significant extent as compared to the hydrophilic polymers; p(HEMA) and p( HPMA). **TH** showed Fickian release mechanism in case of hydrophilic matrices whereas a non-Fickian diffusion was observed with hydrophobic matrix system. However, **PH** was released mainly by Fickian diffusion mechnism except when blended with p(MMA). The effect of diluents on the release of **PH** from p(HPMA) matrix was also studied. The ratio of the drug:diluent:polymer was 0.8:1.2:0.5. $T_{90}$ of 8.30 hr, 10.80 hr and 11.36 hr was observed when lactose, DCP and MCC were used as diluents respectively. No erosion of the tablet was observed. The drug was released through the matrix system. The release was first order with lactose whereas zero order with DCP and MCC. A Fickian diffusion was observed for all these matrix systems containing different diluents.

***TABLE 4: Accelerated Stability Studies***

| Composition (Drug:polymer) | | Release Kinetics 37°C | 45°C | 60°C | 75%RH |
|---|---|---|---|---|---|
| **PH: p(HPMA)(100%)** 0.8: 1.0 | n = | 0.38 | 0.48 | 0.33 | 0.34 |
| | T90 (hr) | 10.83 | 9.32 | 9.56 | 10.23 |
| **PH: p(MMA)(100%)** 0.8: 1.0 | n = | 0.49 | 0.45 | 0.48 | 0.51 |
| | T90 (hr) | 17.82 | 17.32 | 16.39 | 17.91 |
| **TH:(MMA:HPMA)(50%:50%)** 1.0: 1.0 | n = | 0.52 | 0.53 | 0.59 | 0.53 |
| | T50 (hr) | 13.92 | 12.89 | 11.72 | 14.20 |
| **TH:(MMA:HPMA)(10%:90%)** 1.0: 1.0 | n = | 0.49 | 0.51 | 0.53 | 0.54 |
| | T50 (hr) | 5.80 | 5.73 | 5.02 | 6.31 |

**Stability Studies**:

Formulations stored under exaggerated conditions of temperature and humidity showed no significant change in their physical appearance and drug content.

At 45°C & 60°C, tablets showed increase in hardness. Faster release was observed in case of formulations at 60°C and slow release at 75% RH. All formulations exhibited good stability.

## *CONCLUSIONS*

Matrix tablets containing hydrophobic polymers showed a more sustained effect as compared to those containing hydrophilic polymers. All the formulations showed acceptable stability coupled with a good controlled release profile. Hence these polymers can be used effectively when a pH dependent release is required.

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