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Formulation and Evaluation of Oral Sustained Release Suspensions Using Ethyl Cellulose Microcapsules Containing Propranolol Hydrochloride Using Ion Exchange Resinates

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Ethyl cellulose coated ion exchange resinates of propranolol hydrochloride were prepared using amberlite IR 120 by solvent evaporation method. Among 5 batches of microcapsules (drug resinate-ethyl cellouse in ratio 1:1, 1:1.5, 1:2, 1:2.5 & 1:3), prepared an ideal batch (drug resinate-ethyl cellouse ratio 1.0:2.5) was selected for the formulation of sustained release suspension. 8 Batches of suspension were prepared using methyl cellulose and carboxyl methyl cellulose as suspending agents in 4 different concentrations (0.5, 1, 1.5 and 2 %). These suspensions were evaluated for physical stability (by determination of sedimentation volume), redispersibility and *in vitro* release patterns. The results showed that suspensions prepared with carboxyl methyl cellouse had better physical stability than those prepared with methyl cellulose and suspensions prepared with 1.5 carboxyl methyl cellouse as suspending agent showed optimum release and was found to ideal sustained release formulation.

Key Words: Ion exchange resinate, Propranolol, Amberlite IR120, Sustained release suspension.

INTRODUCTION

The goal of any drug release systems is to provide a therapeutic amount of drug to the proper site in the body, to achieve and maintain the desired drug concentration at the site of action[1]. This objective points towards to most important aspects of drug delivery, namely spatial placement and temporarily delivery of the drug. The sustained release system induces any drug delivery system that achieves slow release of drug over an extended period of time. If the system is successfully maintaining a constant drug level in blood or targeted tissue, it is considered as controlled release system. An oral sustained release suspension could be the best suitable

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dosage form for the geriatric patients, because of the easiness of swallowing and flexibility in the administration of the dosage. Many therapeutic benefits could be gained by incorporating functions of sustained drug release into suspension dosage forms. They include improvement of rate and extent of drug absorption, the higher patient compliance, reduce the side effects and taste masking for bitter drugs[2,3].

Propronaolol hydrochloride has great utility as therapeutic agent in the treatment of hypertension. It has short plasma half-life (2-3.5 h) and is metabolized exclusively by first pass metabolism, if incorporated in a sustained release dosage form, only small fraction of the dose would be expose to the first pass metabolism, this can improve the patient compliance and reduce the dose. The different methods for sustaining the release of drugs are described by ariens[4]. One of the methods to sustain the drug release is the use of ion exchange resins. In the present work, propronaolol hydrochloride was absorbed on cationic exchange resin, Amberlite IR-120 and later a coating of ethyl cellulose was given. Then these resonates was formulated into a suspension form, which can release the drug in a slow controlled manner. The dissolution rate and bio-availability from suspensions are reported to the adversely affected by the suspending agents, which are used to increase the viscosity of the media to maintain uniform dispersion during storage[5,6].

In the present study an attempt is made to evaluate different suspending agents for their stability for the formulation of sustained release suspension containing propronaolol hydrochloride microcapsules.

EXPERIMENTAL

Propronaolol hydrochloride was obtained as free samples (Ranbaxy, Bangalore) Amberlite IR120 (BDH, UK), ethyl cellulose (Ranbaxy, Bang lore) methylcellulose and carboxymethylcellulose (SD fine chemicals Chennai), all of the analytical reagent grade were used.

Preparation of drug resinates: The resin beads were grounded and passed through sieve number 120 to get a uniform size distribution. 1 g Of resin was added to 25 mL of propronaolol hydrochloride solution (20 gm/mL) and stirred for 4, filtered and dried.

Determination of ion exchange capacity: The ion exchange capacity of the resin was determined by known quantity of drug resinates with 50 mL of 0.2 M hydrochloric acid for 4 h. It was then filtered and the amount of drug present in the filterate was determined by UV spectrophotometer (Shimadzu 160-A Japan) at 290 nm against a blank, which was prepared under similar conditions using a plain resin.

Preparation of microcapsules: Microcapsules of propranolol hydrochloride resinates were prepared by solvent evaporation techniques[3]. A

known quantity of the drug resinate was dispersed in 100 mL of cyclohexane containing 3% poly isobutylene. To this 35 mL of light liquid paraffin was added and stirred. Sufficient quantity of ethyl cellulose was dissolved in 100 mL of ethyl acetate separately and this polymeric solution was added to the drug resinate dispersion and stirred at 100 rpm until to evaporate the solvent to half of its original volume (120 mL). The microcapsules formed were washed with 25 mL of cyclohexane to remove the excess of poly isobutylenes, followed by washing with 25 mL of petroleum ether to remove the liquid paraffin. The mass was dried and passed through a standard sieve, packed in well-closed container and stored in desiccators. In the present study 5 batches of microcapsules corresponding to drug resinate polymer ratios of (1:1, 1:1.5, 1:2, 1:2.5 and 1:3), coded as N1, N2, N3, N4 and N5, respectively were prepared and evaluated for the drug content, particle size and *in vitro* drug release.

Determination of drug content in microcapsules: A known quantity of (100 mg) of the microcapsules were stirred with 100 mL of 0.2 M hydrochloric acid for 6 h, filtered and the absorbance of the filtrate was measured with spectrophotometrically at 290 nm. The drug content was calculated using the calibration curve.

Determination of the particle size of microcapsules: A small amount of prepared microcapsules was diluted with petroleum ether. Using this suspension, the particle size was determined by optical microscopic method.

***In vitro* drug release from the microcapsules:** From the determination of *in vitro* drug release, USP dissolution Apparatus 2 (paddle method) was used. Half dilution method was employed to maintain different pH conditions in the dissolution studies[7-9]. The prepared microcapsules equivalent to 40 mg of propranolol hydrochloride were added in the 900 mL of buffer solution of pH 1.2, contained in the dissolution flask and the temperature was maintained at 37 ± 1ºC. stirring was done at 100 rpm using the paddle. An aliquote (5 mL) were withdrawn at specific time intervals and equal amount of fresh media was replaced after each sampling. At the end of 3 h half of the medium (that is 450 mL) was removed by filtering through a membrane of 0.45 μm pore size and it was replaced by buffer of pH 9.3, to get a pH of 6.8 in the dissolution medium. The dissolution was continued in this medium upto 12 h. The amount of drug dissolved was determined by diluting the samples with suitably and measuring the absorbance at 290 nm using UV spectrophotometer (Shimadzu160-A Japan).

Preparation of suspensions: The suspensions were prepared by using deionized water as vehicle. The other ingredients added to the formulation were liquid glucose (30 %) and sodium salts of methyl paraben (0.18 %). 8 Batches of suspensions were prepared using 2 suspending agents, namely, methyl cellulose, and corboxy methyl cellulose in 4 different concentra-

tions, 0.5, 1, 1.5 and 2 %. These suspensions were coded from P1 to P8 (Table-2) in all the suspensions. The dose level of propranolol hydrochloride was kept 40 mg per 5 mL of suspension (microcapsules of drug resinates equivalent to 40 mL of the drugs were suspended in each 5 mL).

Physical stability and redispersibility of suspensions: The formulated suspensions were evaluated for physical stability by determining the sedimentation volume[8,10,11]. 50 mL of each suspensions was taken in a 50 mL stopped graduated measuring cylinder. The suspensions was dispersed thoroughly by moving ups and down 3 times. Later, the suspensions were allowed to settle for 2 min and the volume of each sediment was noted. This is the original volume of sediment (H_0) the cylinder was kept undisturbed for 7 d. The volume of sediment read on the 7th day was considered as final volume of sediment (H_0). The redispersibility of the suspensions was checked by moving the stoppered cylinders upside down until there was no sediment at the bottom of the cylinder.

Drug leaching into the suspensions: The amount of the drug leaching into the vehicles after storage of suspensions at room temperature for three months was determined by filtering the suspension and measuring the absorbance at 290 nm, using a suspension prepared with out microcapsules as a blank. The drug leached into vehicle was calculated using calibration curve.

***In-vitro* release from drug suspension:** *In vitro* release studies for the suspensions were carried out by dialysis bag method[4]. Dilution method was employed to maintain different pH condition in the dissolution studies. The suspensions were placed in a dialysis bag and held in a position in the dissolution fluid by a heavy clamp with the stirring element (paddle), which was rotated at 50 rpm. The sampling was done at different intervals and fresh medium was added as replacement for sample quantity. The dissolution was carried out for 12 h, the first 3 h under gastric pH (1.2 pH) followed by 9 h under intestinal pH (pH 6.8) the sample were withdrawn and diluted, the absorbance was measured at 290 nm.

RESULTS AND DISCUSSION

Five batches of microcapsules (N1-N5) propranolol hydrochloride, corresponding to drug polymer ratios of 1:1, 1:1.5, 1:2, 1:2.5 and 1:3 were evaluated for percentage yield, the content particle size and *in vitro* drug release profile. The drug loading capacity of ion exchange resin was found to be 41.65 % w/v. The uniformity of drug content was observed in all the batches and the values of drug content were found to be satisfactory. These values are shown in Table-1. The average particle size for N1-N5 was found to be suitable for formulation of suspensions.

TABLE-1
PHYSICAL CHARACTERISTICS OF MICROCAPSULES

Batch code	Drug resinate polymer ratio	Nature of microcapsules	Yield (%)	Drug content (%)	Average particle size(um) ± SD
N1	1:1	Free flowing	86.54	41.06	233.4 ± 0.107
N2	1:1.5	Free flowing	83.33	40.86	232.9 ± 0.102
N3	1:2	Free flowing	90.27	40.96	239.5 ± 0.107
N4	1:2.5	Free flowing	91.27	41.65	194.9 ± 0.261
N5	1:3	Free flowing	94.31	40.57	227.0 ± 0.402

The *in vitro* drug release studies for different batches for microcapsule (Fig. 1) showed that increase in methylcellulose proportion reduce the rate of release. The batch N5, in which the maximum ethyl cellulose was used, showed minimum drug release (65 %) at the end of 12 h. The batch N1, in which minimum proportion of ethyl cellulose was used, showed maximum drug release (96.9 %). Among the 5 batches, batch N4 showed uniformity of drug release up to 12 h and was considered as ideal for formulation of sustained release suspensions and the batch was selected for further studies.

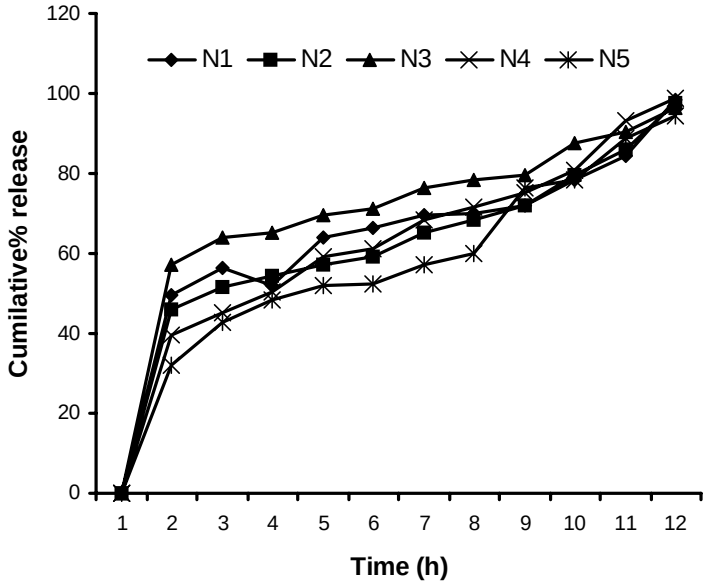

Fig.1: *In vitro* dissolution profile of different batches of microcapsules containing propranolol hydrochloride resinates

Evaluation of suspensions: Eight batches of suspensions of propranolol hydrochloride microcapsules were prepared (P1-P8) and evaluated for physical stability, drug leakage, viscosity and *in vitro* drug release the H_u/H_0 values for the suspensions are shown in Table-2; carboxymethyl

cellulose shown better physical stability than methyl cellulose. The maximum physical stability was obtained with 2 % concentration of both suspending agent. All the suspensions, except those prepared with 2 % of both the suspending agents could be redispersed easily after the seventh day of settling and gave a uniform dispersion upon checking. The suspensions prepared with 2 % concentration of methylcellulose and carboxy methylcellulose could not be redisperse because of their higher viscosity. In all the suspension the drug leaching was found to be less than 0.1 % after storing them at room temperature for 3 months, which provide the protection offered by ethyl cellulose.

TABLE-2
PHYSICAL CHARACTERISTICS OF AND DRUG LEACHING IN DIFFERENT BATCHES OF SUSPENSIONS PREPARED USING PROPRANOLOL HYDROCHLORIDE RESINATES

Batch code	Suspending agent	Concentration % w/v	Viscosity (cps)	H_u/H_0	Amount of drug released into vehicle (%)
P1	Methyl cellulose	0.5	200	0.40	0.09
P2	Methyl cellulose	1.0	290	0.70	0.06
P3	Methyl cellulose	1.5	240	0.73	0.05
P4	Methyl cellulose	2.0	350	0.80	0.06
P5	Carboxymethyl cellulose	0.5	230	0.40	0.07
P6	Carboxymethyl cellulose	1.0	280	0.84	0.05
P7	Carboxymethyl cellulose	1.5	300	0.85	0.04
P8	Carboxymethyl cellulose	2.0	380	0.86	0.04

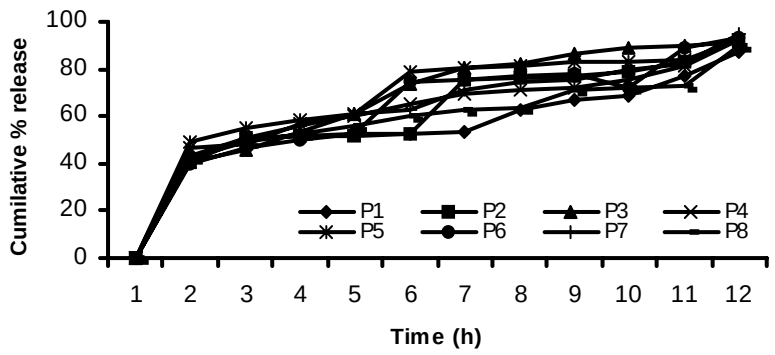

Fig.2 : *In vitro* dissolution profile of different batches of suspensions

The results of *in-vitro* studies are shown in Fig.2. The release data showed that the rate of drug release from the suspension were reduced with the increasing the concentrations of suspending agents. This is because of the reason that an increasing concentration of suspending agent

increases viscosity, which in turn reduces the rate of diffusion. The suspension prepared with 2% concentration of methylcellulose and carboxymethyl cellulose shown maximum sustaining effect and released only 79.01 and 71.43 % of drug at the end of 12 h. But the physical characteristics of that suspension were not ideal. The suspensions were prepared with 1.5 % of suspending agents as good physical stability and redispersability[12]. The release pattern was also suitable for a sustained release preparation. Hence, they were considered as ideal.

Conclusion

Propranolol hydrochloride ion exchange resinates coated with ethyl cellulose was formulated, as oral suspension is an effective system for sustain release of propranolol hydrochloride. This can be a suitable dosage form for geriatric patients because of the easiness of swallowing and flexibility in the administration of the dosage.

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