Development of Sustained Release Suppositories of Terbutaline Sulphate

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Terbutaline-loaded conventional suppositories, sustained release matrix suppositories and sustained release two layered suppositories were prepared using Polyethylene glycol 4000, Drug Coat L100 and Drug Coat S100. *In vitro* characteristics of these suppositories were evaluated. In comparison to conventional suppositories the release of drug from sustained release matrix suppositories was gradual and extended over a period of time. On the other hand two layered suppositories produced an initial quick release followed by extended release of the drug.

Terbutaline sulphate (TS), a selective β_2 agonist, is used in the treatment of bronchial asthma. Therapeutic level of TS in plasma for an extended period of time is desired in nocturnal asthmatics, so that patient can have undisturbed sleep particularly at night[1]. Because of extensive first pass metabolism, the bioavailability of TS, following oral administration, is much less (14±2%) and the onset of action may be delayed for 1-2 h[2]. It is well known that rectal route can deliver 60-70% of the administered drug directly into the systemic circulation[3,4] and thus avoids loss of drug due to the first pass effect. With this view, the present study aims at the development and evaluation of sustained release matrix and two layered suppositories prepared with polyethylene glycol (PEG) 4000 and methacrylic and methylmethacrylate copolymers like drug coat L100 and drug coat S100.

Turbutaline sulphate was obtained from Themis Pharmaceuticals, Mumbai. Drug coat L100 and S100 were donated by Harekrishna Polymers, Mumbai. PEG 4000 was purchased from S.D Fine Chemicals, Mumabi. All other analytical grade chemicals were procured commercially and were used as received.

Terbutaline-loaded conventional suppositories (CS) were prepared using PEG 4000 as base in a stainless steel mold of 1g capacity by fusion method[5]. Sustained release matrix suppositories (SMS) were prepared using PEG 4000 and variable amount (10 and 15%) of drug coat L100 (DL100) and drug coat S100 (DS100) by solid dispersion technique following the method of Ohinshi *et al*[6]. Sustained release two layered suppositories (STLS) were prepared by casting SMS over CS in the molds. The theoretical drug load in each of the suppositories was 10 mg.

In vitro and *in vivo* liquifaction time of the suppositories were determined following the method previously reported[7]. *In vitro* release of drug from CS, SMS and STLS were monitored in phosphate buffer (pH 7.2) solution following the method reported earlier[7]. Suppositories were placed in a dialysis tubing (previously soaked in water for 24 h) and were then, placed in 30 ml phosphate buffer pH (7.2) at 37±1°. Samples were withdrawn at predetermined time intervals and were analysed spectrophotometrically at 550 nm[8] (Beckman UV-Vis double beam spectrophotometer model DV64).

The average weight and the actual drug content of terbutaline loaded conventional suppositories (CS) and sustained release matrix suppositories (SMS) prepared with DL100 and DS100 have been represented in Table 1. The average weight of SMS containing variable amount of DL100 and DS100 did not vary appreciably from the average weight of CS. Further, the actual drug content of both CS and SMS containing variable amount of DL100 and DS100 were similar to the theoretical drug loading.

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TABLE 1: AVERAGE WEIGHT AND ACTUAL DRUG CONTENT OF TERBUTALINE-LOADED SUPPOSITORIES

	Conventional Suppositories	Matrix Suppositories Containing			
		Drug Coat L100		Drug Coat S100	
		10%	15%	10%	15%
Average wt (g) (mean±SD)	0.95 (±0.02)	0.98 (±0.02)	0.92 (±0.07)	0.96 (±0.02)	0.92 (±0.03)
Drug Content (mg) (mean±PD)	10.72 (±0.15)	10.28 (±0.24)	10.89 (±0.27)	9.99 (±0.41)	10.50 (±0.40)

Theoretical drug load for each suppository was 10 mg. Average weights are for 10 observations and drug contents are mean of 6 observations, SD and PD denote standard deviations and percentage deviations, respectively.

These observations indicate the simplicity and reproducibility of the method of preparation and homogenity of the suppositories.

Estimation of *in vitro* liquifaction time showed that about 70% of the suppository mass from all the suppositories (CS, SMS, STLS) were liquified at about 30 min and 100% were liquified within 65 min, and no palpably core was noticed.

In vitro liquifaction time correlated well with *in vitro* results. The release profiles of terbutaline sulphate from different suppositories have been represented in fig. 1. It was revealed that while the time required for 50% release of drug ($t_{50\%}$) from conventional suppository was 2.5 h, $t_{50\%}$ from matrix suppositories containing 10% DL100 and DS100 were 5 and 8 h, respectively. On the other hand, $t_{50\%}$ for sustained release two layered suppositories were 4.25 and 6.5 h, respectively. This indicated that release of the drug from either SMS or STLS containing DS100 was much more prolonged when compared with either CS or SMS and STLS containing DL100. This was due to presence of lower content of quarternary ammonium group in DS100 than in DL100. Moreover, STLS provided faster release than SMS since one of the layers of STLS was CS which provided higher initial release. Similar observations were noted in suppositories containing 15% DL100 and DS100 (fig. 2).

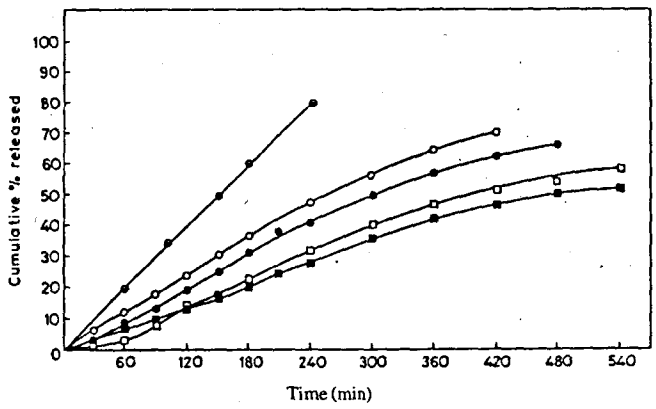

Fig. 1: Dissolution profile of terbutaline

Dissolution profile of terbutaline was determined in pH 7.2 phosphate buffer from conventional (◒), matrix suppository (10%, DL100) (O), matrix suppository (10% DS 100) (□), two layered suppository (10% DL 100) (O), two layered suppository (10% DS100) (□) having drug distribution in two layers 1:1

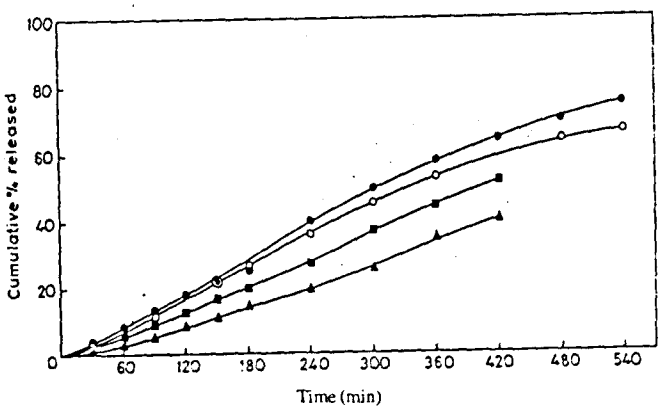

Fig. 2: Dissolution profile of terbutaline

Dissolution profile of terbutaline was determined in pH 7.2 phosphate buffer from matrix Suppository (15% DL 100) (O), matrix suppository (15% DS100) (▲), two layered suppository (15% DL100) (O), two layered suppository (15% DS100) (□) having drug distribution in two layers 1:1.

In conclusion, sustained release two layered suppositories (STLS), prepared in this study, could be a very useful dosage form for the treatment of asthma, particularly for nocturnal attack. Drug coat L100 and drug coat S100 could be good substitutes for eudragit which is widely used as a drug retarding agent.

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Development of Dissoulution Medium for Rifampicin Sustained Release Formulations

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Dissolution of drugs from solid dosage forms is a key parameter during the product development, formulation and through out the product storage. Rifampicin is very stable in the solid state. Rifampicin transforms into rifampin quinone in mildly alkaline solutions and in presence of atmospheric oxygen at room temperature. The main decomposition product of rifampicin in aqueous acidic medium was 3-formyl rifampicin SV. The decomposition of rifampicin in aqueous solution is diminished by the addition of reducing agents such as ascorbic acid and sodium ascorbate. In USP, 0.1 N HCl is an official dissolution medium and the amount of rifampicin was estimated in comparison with a standard solution having a known concentration of rifampicin concomitantly held at the same temperature for the time specified. This is not suitable for studying release kinetics of controlled release formulations. For this reason, stability of rifampicin in different aqueous fluids and buffers of varying pH in the presence of ascorbic acid as reducing agent was studied. The results indicated that rifampicin was more stable in phosphate buffer of pH 7.4 containing 0.02% w/v of ascorbic acid. Drug release studies of commercial products were done by using this medium and they were compared with the official USP method. This medium was found to be more suitable for studying rifampicin controlled release formulations.

Dissolution of drugs from solid dosage form is an important parameter in assessing the release rate, its mechanism and kinetics during product development. It is also essential for ensuring the product content and uniformity at the formulation stage as well as during its storage. It is important to accept any method of analysis that the analysate is not affected during analysis. For drugs such as rifampicin in aqueous solution, either acidic

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