Controlled Release HPMC Matrix Tablets of Propranolol Hydrochloride

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Propranolol hydrochloride matrix tablets were prepared with hydroxypropyl methylcellulose polymer to control the release of drug with a view to develop twice daily sustained release dosage form. The resulting matrix tablets prepared with hydroxypropyl methylcellulose K4M fulfilled all the official requirements of tablet dosage forms. The *in vitro* drug release was measured in aqueous solutions for a total period of 12 h using 1.2 pH buffer for first 1 h and pH 7.5 buffer for the rest of period. The drug release was within the limits of predetermined set vis-à-vis USP requirements. The results provide a method of achieving sustained drug action through uniform drug release.

Propranolol hydrochloride is a widely used antihypertensive agent with non-selective β-adrenergic receptor antagonist activity. It is almost completely absorbed from the gastrointestinal tract, but is subject to considerable hepatic tissue binding and first-pass metabolism[1]. Biological half life is about 4 h. Short biological half life and first-pass metabolism favour pharmacokinetic rationale for sustained release. Propranolol hydrochloride conventional release tablets are administered 20 to 40 mg 3 to 4 times daily in the management of several cardiovascular disorders such as hypertension, angina pectoris and arrhythmias[2]. However, the therapy with conventional tablets is associated with fluctuations of the drug plasma levels and is inefficient. An effort was therefore, made to develop a simple and effective sustained release propranolol hydrochloride tablets using polymer matrix system with uniform *in vitro* release properties. Hydroxypropylmethylcellulose (HPMC) is the dominant hydrophilic vehicle used for the preparation of oral controlled drug delivery systems[3]. The transport phenomena involved in drug release from HPMC matrices are complex, because the micro and macrostructure of HPMC exposed to water is strongly time dependent. Upon contact with gastrointestinal fluid, HPMC swells and finally dissolves[4]. Narasimhan and Peppas[5] showed that the dissolution can be either disentanglement or diffusion controlled depending on the molecular weight and thickness of the diffusion boundary layer. The rate of polymer swelling and dissolution as well as the corresponding rate of drug release are found to increase with either higher levels of drug loading or lower viscosity grades of HPMC[6]. To sustain drug release, it is important to obtain control release properties. It was considered that HPMC matrix tablet having a fixed area may provide more control release property. It was the aim of this study to develop sustained release propranolol hydrochloride dosage form and to evaluate the resulting drug release kinetics from HPMC matrices.

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Propranolol hydrochloride was obtained from New Drug and Chemical Company, Mumbai. HPMC K4M (a grade of HPMC) was procured from Colorcon Asia Pvt. Ltd., Mumbai. PVP K30 (polyvinyl pyrrolidone K-30) and lactose were purchased from Coveral and Company, Chennai. Magnesium stearate and talc were procured from Mohanlal Dayaram and Company, Hyderabad. All other ingredients used throughout the study were of analytical grades and were used as received.

The mathematical description of drug release that follow zero order kinetics is based on the equation[7] $k_r^0 = k_e C_d V_d$ where, k_r^0 is the zero order rate constant for drug release, k_e is the first order rate constant for overall drug elimination, C_d is the desired drug level in the body and V_d is the volume space in which the drug is distributed. For propranolol hydrochloride $t_{\frac{1}{2}}$=4h[8], V_d =310.8 l/70kg (4.08 to 4.82 l/kg)[9] and C_d =0.075 μg/ml (50 to 100

TABLE 1: FORMULA OF PROPRANOLOL HYDROCHLORIDE MATRIX TABLETS

Name of the component	Weights	
	Unitary (mg)	Batch (kg)[a]
Propranolol hydrochloride	80	0.24
HPMC K4M	80	0.24
Lactose	120	0.36
PVP K30	8	0.024
Magnesium stearate	6	0.018
Talc	6	0.018
TOTAL	300	0.90

a-batch of 3000 tablets

ng/ml)[10] and therefore the drug release rate can be calculated using the formula $k_r^0 = 0.693/4 \times 310.8 \times 0.075 = 4.04$ mg/h Hence the total dose (DT) for sustaining 12 h can be calculated using the equation DT=DI–TP+DS = mg-(2 X 4.04+12 x 4.04 mg=80.4 mg ($\cong$ 80 mg). Where, DI is the initial dose (i.e. conventional dose=40 mg), TP is the amount of drug release from sustained dose (DS) during release of initial dose for 2 h and DS is the sustained dose for 12 h.

Matrix tablets were prepared by wet granulation method. The composition of the formulation is given in Table 1. The composition with respect to polymer: drug ratio of 1:1 was selected based on trial preparation of tablets. The drug polymer ratio and the formula was developed to adjust drug release as per predetermined limits (to be mentioned latter) under experimental conditions of preparations. Propranolol hydrochloride (0.24 kg), lactose (0.36 kg) and HPMC K4M (0.24 kg) were mixed in a polybag and the mixture was passed through a mesh No. 60. Granulation was done with a solution of 0.024 kg of PVP K30 in sufficient isopropyl alcohol. The wet mass was passed through a mesh No. 12. The wet granules were dried at 50° for about 2 h. The dried granules were sized by a mesh No. 18 and mixed with magnesium stearate (0.018 kg) and talc (0.018 kg). Granules thus obtained, weighing equivalent to 300 mg, were compressed into tablets on a 16 station Cadmach single punch tabletting machine (Cadmach Machinery Co. Pvt. Ltd., Mumbai) using 9.5 mm concave punches.

The prepared tablets were divided into two lots. One

TABLE 2: TABLETING CHARACTERISTICS OF PREPARED MATRIX TABLETS FOLLOWING STORAGE

Test	Initial Tablets	Strip pack at 45° with 75% RH		Blister Pack at 45° with 75% RH	
		30 d	60 d	30 d	60 d
Weight[a] (mg)	303 (1.52)	301 (1.75)	302 (1.15)	303 (1.69)	302 (1.26)
Hardness[b] (kg/cm^2)	9.57 (0.21)	9.83 (0.35)	9.63 (0.69)	10.1 (0.68)	9.76 (0.48)
Drug content[b] (%)	99.9 (1.48)	98.9 (1.45)	99.6 (1.76)	99.6 (2.01)	99.2 (1.01)
Thickness[b] (mm)	4.23 (0.06)	4.17 (0.06)	4.20 (0.07)	4.20 (0.07)	4.23 (0.05)
Friability[c] (%)	0.35	0.30	0.23	0.26	0.36

Figures in the parentheses represent ±SD; a-mean (±SD), n= 10; b-mean (±SD), n=6; c-10 tablets

TABLE 3: *IN VITRO* DRUG RELEASE OF MATRIX TABLETS

Time (h)	Cumulative % drug released				
	Initial Tablets	Strip pack at 45° with 75% RH		Blister Pack at 45° with 75% RH	
		30 d	60 d	30 d	60 d
1	17.40	18.23	16.50	16.25	15.75
3	38.96	38.32	37.95	38.10	38.50
6	57.99	57.82	60.45	58.90	59.45
12	87.81	88.21	90.50	90.25	91.95

each of lot is packaged in strip pack and in blister pack. The strip pack was made of two layers of film. The blister pack was PVdC (polyvinyidene chloride–0.028 mm thickness)/ aluminium foil (0.02 mm thickness). The strip and blister packaged samples were stored at 45° with 75% RH. Samples were withdrawn at 0, 30 and 60 d for evaluation.

All the tablets (both packs and at end of 30 and 60 d) were tested as per standard procedure for weight variation, hardness, drug content, thickness and friability and *in vitro* drug release characteristics. Two samples of tablets (strip and blister packaged after 60 d of storage) were subjected to detailed dissolution studies. Hardness of the tablets was determined by using a Schleuniger tablet hardness tester. Friability test was conducted using a Roche friabilator. Thickness of the tablets was measured by Vernier calipers. Drug content for propranolol hydrochloride in dilute hydrochloric acid was carried as per USP[11] by measuring the absorbance of samples at 289 nm using a Shimadzu 1201 UV/Vis spectrophotometer and comparing the content from a calibration curve, prepared with USP propranolol hydrochloride RS in same medium.

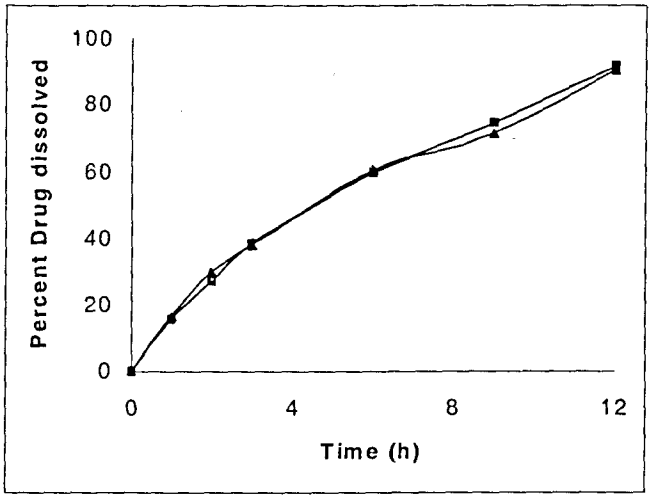

Fig. 1: Dissolution profile of Propranolol hydrochloride from matrix tablets

***In vitro* cumulative release of propranolol hydrochloride from sample of strip pack after storage for 60 d (– ▲ –) and that of blister pack (– ◘ –)**

Drug release was studied using USP 24 basket dissolution apparatus. Dissolution test was carried out for a total period of 12 h using pH 1.2 buffer solution (900 ml) as dissolution medium at 37±0.5° and at 50 rpm for first 1h and pH 7.5 buffer for the rest of the period. Ten millilitres of the sample was withdrawn at regular intervals and replaced with the same volume pre-warmed (37±0.5°) fresh dissolution medium. The samples withdrawn were filtered and drug content in dissolution medium in each sample was analyzed after suitable dilution with water by above mentioned spectrophotometer at 320 nm as specified for USP propranolol hydrochloride extended release capsules[12]. The actual content in samples was read from a calibration curve, prepared with USP propranolol hydrochloride RS. The predetermined drug release requirement was set at 1 h (not more than 20%), 3 h (between 20-40%), 6 h (between 45-80%) and 12 h (not less than 80%).

The results of the uniformity of weight, hardness, drug content, thickness and friability of the tablets are given in Table 2. All the samples of tablets prepared fulfilled the official requirements of uniformity of weight. The drug content was found to be within 5% variation of the 80 mg in all formulations thus complying with IP limits for content uniformity. The low friability indicates that the matrix tablets are compact and hard. The hardness was slightly higher than optimum to make tablets compact indicated by low friability.

The results were reproducible, even on tablets after storage indicated by standard deviation (Table 2).

Propranolol hydrochloride release from tablets was studied in acidic (pH 1.2 buffer) and alkaline (pH 7.5 buffer) solutions for a period of 12 h as prescribed for propranolol hydrochloride extended release capsules (test 2) in USP 24. The drug releases were well within limits (Table 3). Release followed near zero order kinetics after a lag period of 2 h (R^2= 0.95). These data observed for two samples after 60 d of storage are shown as a function of time in fig. 1. The release appears to occur in three stages. An initial rapid release occurs for first 2 h, followed by a slow release that is almost linear in line. In the final stage, release slows further, tending to the almost saturation concentration of the drug. The *in vitro* release was extended over a period of more than 12 h. These results reveal that HPMC matrix tablet is useful for making an effective sustained release dosage form to achieve a desired release. It may be concluded that matrix system using suitable grade of HPMC polymer is a suitable delivery system for propranolol hydrochloride and can help to reduce dose of drug and frequency (twice daily).

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Synthesis and Antimicrobial Screening of Novel Mannich Bases of Isatin Derivative

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A new series of N-Mannich bases (Ia-Ih) of 3-semicarbazino isatin (I) was synthesized by reacting (I) with formaldehyde and various aromatic primary amines. The chemical structures were confirmed by means of IR, ^{1}H NMR and elemental analysis. The compounds synthesized were screened for antimicrobial activity against *Staphylococcus aureus*, *Escherichia coli* and *Candida albicans* by

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