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RESEARCH ARTICLE

FORMULATION AND EVALUATION OF ONCE DAILY SUSTAINED RELEASE MATRIX TABLET OF VERAPAMIL HYDROCHLORIDE

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ABSTRACT

Matrix tablets of Verapamil Hydrochloride were formulated as sustained release tablet employing sodium alginate, hydroxyl propyl methyl cellulose polymer, Ethyl cellulose and the sustainedrelease tablets was investigated. Sustained release matrix tablets contain 240 mg Verapamil Hydrochloride were developed using different drug polymer concentration of HPMC, Sodium Alginate and Ethyl Cellulose. Tablets were prepared by wet granulation using HPMCand water solution. Formulation was optimized on the basis of acceptable tablet properties and *in-vitro* drug release. The resulting formulation produced robust tablets with optimum hardness, thickness consistent weight uniformity and low friability. All tablets but one exhibited gradual and near completion sustained release for Verapamil Hydrochloride, and 99% to 101% released at the end of 24 hrs. The results of dissolution studies indicated that formulation F8, the most successful of the study. An increase in release kinetics of the drug was observed on decreasing polymer concentration.

Key words: Verapamil Hydrochloride, Sustained Release, Hydroxyl Propyl Methyl Cellulose, Sodium Alginate, Ethyl Cellulose

INTRODUCTION:

A number of methods and techniques have been used in the manufacturing of oral extended release dosageforms. Probably the simplest and least expensive way to control the release of an active agent is to disperse it in an inert polymeric matrix. In polymeric system, the active agent is physically blended with the polymer powder and then fused together by compression moulding, which is a common process in the pharmaceutical industry. These dosage forms are designed to deliver the drug at a controlled and predetermined rate, thus maintaining a therapeutically effective concentration of the drug in the systemic circulation for a long period of time and therefore reducing the frequency of dosing and improving patient compliance. Hydrophobic materials for an insoluble matrix carrier and water-soluble hydrophilic materials have been reported as the most commonly used matrix carriers.[1]Verapamil HCl is a water-soluble phenyl-alkyl amine derivative, which has been used widely in the treatment of the hypertension, angina pectoris and arrhythmias.[2,3] Hydrophilic matrix tablets offer precise modulation of drug release through manipulation of a small number of formulation factors[4]. Hydroxypropylmethylcellullose (HPMC), is a hydrophilic polymer which is used to control drug release from several pharmaceutical systems because of its non-toxic nature, easy compression, swelling properties and accommodation for high levels of drug. In HPMC matrix systems, drug release profiles are strongly influenced by the kind of polymer, its proportion in the formulation and its viscosity grade[5]. However, fillers which are used in these systems play a significant role on drug release. While the addition of a soluble filler (*i.e.* lactose) to HPMC matrix systems increases porosity which leads to rapid diffusion of drug and also increases the rate of the polymer erosion which results in acceleration of drug release, the addition of an insoluble filler (*i.e.* calcium phosphate dihydrate) can inversely effect the release of drug from these systems dependent on its level[6]. HPMC and lactose combinations to form an erodible hydrophilic gel matrix system have previously been used successfully to produce controlled release preparations[7]. However, swollen hydrophilic matrix systems have generally showed a nearly first order drug release profile. In hydrophilic matrix systems, the dissolution of the drug present at the surface of the matrix causes an initially high release rate of drug, followed by a rapidly declining drug release rate due to swelling and consequent increasing of the dissolution path-length of the matrix[8-12]. To overcome this undesirable behavior, various matrix geometries have been recommended to achieve an almost constant release rate of drug with time. One of these techniques relies on the use of multi-layered matrix tablets as a drug delivery device[13]. Multi-layered matrix tablet is a drug delivery device, which comprises a matrix core containing the active solute and one, or more barriers (modulating layers) incorporated during the tabletting process. A three-layered matrix tablet consists of drug core layer sandwiched by the external modulating layers. The modulating layers which contain a hydrophilic polymer, usually HPMC[14], delay the interaction of active solute with dissolution medium, by limiting the surface available for the solute release and at the same time controlling solvent penetration rate[15-17]. Thus burst effect can be smoothened and the release can be maintained at a relatively constant level during the barrier layers` swelling and erosion process. When the swollen barriers are erosion dominated the surface available for drug release slowly increases[16].By this way, combining a time-dependent control of the hydration rate of the device with the reduction of tablet surface exposed to the dissolution medium, it is feasible to achieve a linear drug release profile. Some of the advantages of three-layered matrix systems include the maximum flexibility in drug release patterns, ease of manufacturing, total system solubility and total release of drug[13,18,19].

MATERIALS AND METHODS

Verapamil hydrochloride was obtained from Cadila Pharmaceutical Limited, Dholka, HPMC E4M, a grade of HPMC, was procured from Dow Chemical Company, Microcrystalline cellulose, was procured from FMC Biopolymer,Lactose monohydrate was procured from DMV-Fonterra, Magnesium stearate was procured from Ferro Corporation. Materials and excipients used in preparing tablets. All other ingredients used throughout the study were of analytical grade and were used as received.

Preparation of matrix tablets:

Matrix tablets, each containing 240 mg Verapamil Hydrochloride, were prepared by wet granulation technique. The drug polymer concentration was developed to adjust drug release and to keep total weight of tablet constant for all the fabricated batches under experimental conditions of preparations. The total weight of the matrix tablets was 430 mg with different drug polymer (HPMC, Sodium Alginate, EthylCelluose) concentration. A batch of 500 tablets was prepared in each formula. The composition of tablets is shown in Table 1. Lactose monohydrate and Microcrystallinecellulose was incorporated as diluent excipient to maintain tablet weight constant. The ingredients Verapamil Hydrochloride, HPMC, Lactose monohydrate and Microcrystalline cellulosewere passed through sieve no. 20 and mixed in a polybag for 10 minutes. The powder blend was granulated using granulating fluid HPMC 5cps dissolved in Purified water with constant stirring using glass rod till clear solution. Mill the wet granules through multimill by using 5.0 mm screen at medium speed and knives forward direction. Dry the wet mass in fluid bed drier at ambient temperature initially for 5-10 minutes and then at inlet temperature of 50ºC-60ºC. The dried blend was sifted through sieve no. 16 and retain on sieve no. 16, pass the granules through co-mill by using 2.0 mm screen at 500 – 800 RPM. The granules was then lubricated with magnesium stearatepass through sieve no. 40 and compressed into tablets on a 18-station single rotary machine using 14.50×6.50 mm, capsule shaped punches with bisecting line on upper punch and pain surface on lower punch.

Evaluation of tablets:

The prepared matrix tablets were evaluated for hardness, weight variation, thickness, friability and drug content. Hardness of the tablets was tested using a Portable Digital Hardness Tester(Inwek, Ukraine). Friability of the tablets was determined in a Roche friabilator (Electro Lab). The thickness of the tablets was measured by verniercallipers. Weight variation test wasperformed according to official method. Drug content for Verapamil Hydrochloride was carried out by measuring the absorbance of samples at 278 nm using Shimadzu 1201 UV/Vis spectrophotometer and comparing the drug content from a calibrated curve prepared with standard Verapamil Hydrochloride in the same medium.

In vitro drug release studies:

Drug release studies were carried out according to USP XXVII. pH 1.2 0.1N HCl was used for the first two hours and pH 6.8 phosphate buffer was used for the following 22 hours as dissolution media. USP XXVII-Apparatus II was used at 50 rpm. Withdraw a specimen of 10 ml of solution from a zone midway between the surface of medium and top of the paddle, not less than 1 cm from the vessel wall and add 10 ml of fresh medium in vessel of the apparatus at predetermined time interval. The amount of Verapamil Hydrochloride was determined spectrophotometrically (UV) at 278 nm.The actual content in samples was read from a calibration curve prepared with standard Verapamil hydrochloride.

Stability studies:

In the present work stability study was carried out for the optimized formulation. Optimized batch was strip packaged and kept at 40°C with 75% RH for 3 months. Evaluation of appearance, drug content and in vitro drug release.[20]

Table 1: Formula of Verapamil Hydrochloride Tablet

Ingredients (mg/ml)	Formulations									
	F1	F2	F3	F4	F5	F6	F7	F8	F9	F10
Verapamil Hydrochloride	240	240	240	240	240	240	240	240	240	240
Lactose Monohydrate	19	19	8.5	8.5	8.5	8.5	8.5	8.5	8.5	8.5
Avicel PH 101	28.5	28.5	13	13	13	13	13	13	13	13
HPMC E4M	32	-	77.5	77.5	-	-	-	39	116	51.5
Sodium Alginate	97	97	77.5	-	77.5	39	116	116	39	51.5
Ethyl Cellulose	-	32	-	77.5	77.5	116	39	-	-	51.5
HPMC 5cps	9	9	9	9	9	9	9	9	9	9
Purified Water	q.s.	q.s.	q.s.	q.s.	q.s.	q.s.	q.s.	q.s.	q.s.	q.s.
Magnesium Stearate	4.5	4.5	4.5	4.5	4.5	4.5	4.5	4.5	4.5	4.5

RESULT AND DISCUSSION:

The result of hardness and friability of the prepared matrix tablets ranged from 10 kp to 15 kp and 0.10 to 0.21 respectively. The tablet formulations in all the prepared batches contained Verapamil hydrochloride within 240 ± 5% of labeled content. As such, all the batches of the fabricated tablets were of good quality with regard to hardness, friability and drug content. All tablets complied with pharmacopoeial specifications for weight variation and friability. Verapamil hydrochloride release from tablets was slow and extended over longer periods of time. The results

of dissolution studies of formulations F1 to F10 are shown in fig. 1. Drug release from the matrix tablets was found to increase with decrease in drug polymer concentration.The release of drug depends not only on the nature of matrix but also the drug polymer concentration. As the percentage of polymer increased, the kinetics of release decreased. This may be due to structural reorganization of hydrophilic HPMC and Sodium Alginate polymer. Increase in concentration of HPMC may result in increase in the tortuosity or gel strength of the polymer. When HPMC polymer is exposed to aqueous medium, it undergoes rapid hydration and chain relaxation to form viscous gelatinous layer (gel layer). Failure to generate a uniform and coherent gel may cause slow drug release[12,13]. In vitro release studies demonstrated that the release of Verapamil Hydrochloride from all these formulated matrix tablets can generally be modified (fig. 1). According to commercial tablet, modified release profile of oral controlled release formulation of Verapamil hydrochloride should provide a release of NMT 30% in 1 hr, 35-60% in 4hrs, 55-80% in 8hrs, 70-95% in 14 hrs and 81-105% in 24 hrs. Formulation F8 tablet gave release profile close to the commercial modified release tablet needed for Verapamil Hydrochloride (fig. 1). The data for stability studies carried out for F8 batch at 40°C with 75% RH for 3 months revealed that no considerable differences in drug content and dissolution rate were observed (Table 4). It may be concluded from the present study that slow, controlled and complete release of Verapamil Hydrochloride over a period of 24hrs was obtained from matrix tablets (F8). It is also evident from the results that formulation F8 is better system for once daily SR of Verapamil Hydrochloride.

Table 2: Percentage of drug release

Formulation	Percentage of Drug Release (hrs)								
	1 hr	2 hrs	4 hrs	8 hrs	12 hrs	16 hrs	20 hrs	22 hrs	24 hrs
F1	22.1	36.2	56.2	71.5	86.3	93.6	99.3	-	-
F2	26.3	41.2	61.3	82.1	95.1	99.5	-	-	-
F3	19.2	26.1	42.6	69.5	82.6	93.7	98.9	-	-
F4	19.3	25.2	38.5	55.1	79.3	91.6	99.8	-	-
F5	21.3	38.6	57.8	72.5	85.1	96.2	99.9	-	-
F6	19.1	35.8	51.9	67.2	81.2	91.5	97.8	99.2	-
F7	20.0	38.3	55.1	71.2	85.4	95.8	-	-	-
F8	19.5	31.2	46.5	64.1	77.5	87.3	94.4	97.1	99.3
F9	16.1	26.1	41.5	57.3	72.3	80.6	87.6	90.2	93.4
F10	16.2	25.1	38.1	51.4	63.4	73.2	81.3	85.1	89.9

Table 3: Properties of Compressed Verapamil Hydrochloride Matrix Tablet

Formulation	Weight (mg)	Hardness (kp)	Thickness (mm)	Friability (%)	Drug content (%)
F1	428.9	10.2	5.80	0.13	98.5
F2	434.6	12.3	5.89	0.16	100.2
F3	433.1	12.1	5.85	0.13	98.3
F4	429.3	11.2	5.60	0.19	99.5
F5	431.6	10.5	5.99	0.14	99.0
F6	431.9	11.1	5.91	0.20	98.9
F7	430.9	13.1	5.98	0.13	98.5
F8	431.5	11.9	5.91	0.16	100.1
F9	430.5	12.6	5.88	0.12	98.6
F10	431.1	13.1	5.85	0.15	99.6

Table 4: Stability studies of Formulated F Batch Tablet

Parameter	Initial Tablet	Strip pack at 40ºC/75%RH		
		1 Month	2 Month	3 Month
Drug Content	100.1 %	99.8 %	99.64 %	99.25 %

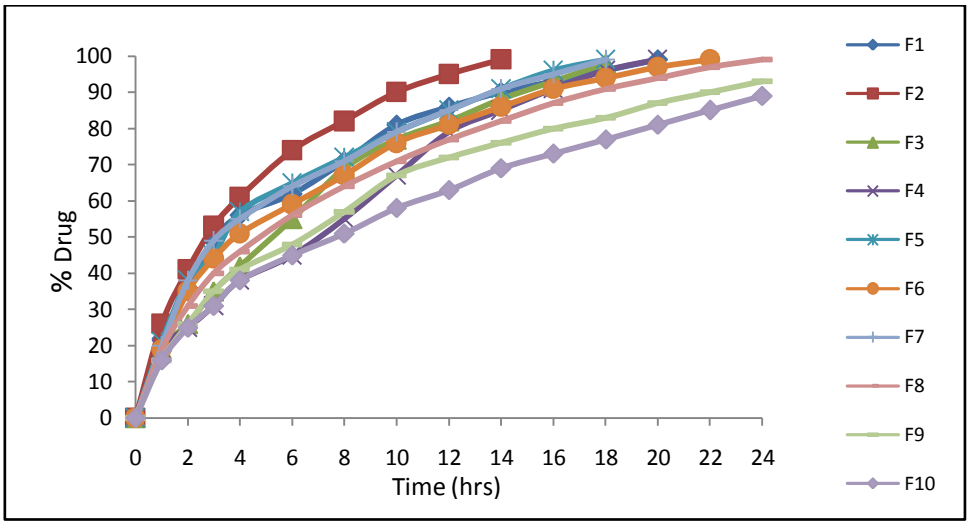

Figure 1: Percentage of drug release

CONCLUSION

In the above view of findings it can be concluded that the combination of different hydrophilic polymer are better suited for site specific drug delivery system than hydrophobic polymer alone. A matrix design of this kind can serve as an alternative strategy to enteric film coating techniques commonly employed for the design of delayed release systems.

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