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Research Article

DESIGN AND *IN VITRO* EVALUATION OF SUSTAINED RELEASE MATRIX TABLETS OF COMPLEXED NICARDIPINE HYDROCHLORIDE

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ABSTRACT

The objective of present work is to develop and characterize an oral sustained release matrix tablet of complexed Nicardipine Hydrochloride by employing hydrophilic and hydrophilic polymers. Due to poor water solubility of the drug its bioavailability is dissolution rate limited. The purpose of the study was to increase the solubility of Nicardipine by cyclodextrin inclusion complex technique. Complexes of different molar ratio were prepared. Kneading method was employed for preparation of inclusion complexes. Among different complexes, a complex with 1:1 molar ratio of drug and β-CD showed the highest dissolution rate. Matrix tablets were prepared by direct compression technique using different concentration of polymers and selected complex. The blended powders and tablets were evaluated for various physico-chemical parameters as per official protocol. The *in-vitro* dissolution study was carried out in acidic medium (pH 1.2) for 2 hrs, followed by phosphate buffer dissolution medium (pH 6.8) for next 12 hrs. The blended powders showed satisfactory flow properties and compressibility. All the tablet formulations showed acceptable pharmacotechnical properties and complied with official specifications. The *in-vitro* release pattern indicated that formulation F7 was good releasing the drug for period of 12 hrs and was best fitted to Higuchi release profile. The present study has demonstrated that combination of hydrophobic and hydrophilic polymers effectively sustained the drug release for prolonged period of time and a minimum of 28 % sodium alginate is required to retard the release of nicardipine from matrix tablet for the period of 12 hours.

Keywords: Nicardipine Hydrochloride, Matrix tablets, Direct compression technique, Sodium alginate.

INTRODUCTION

Drug solubility and dissolution rate are the important physiochemical factors affecting drug absorption from most of the absorption sites. Theinclusion complex [1] approach has been widely and successfully applied to improve the solubility, dissolution rates and consequently the bioavailability of poorly water soluble drugs. Controlled release dosage form [2, 3, 4] has been constantly used to retard the release of therapeutic agent such that its appearance in the circulation is steadily maintained and its plasma profile is prolonged. . It also implies the reproducibility and predictability in the drug release kinetics. The matrix system [5] is the most frequently applied technique among several innumerable methods used in controlled release of drugs from a Pharmaceutical dosage form. It involves the compression of blends of drug, retardant material and additives to form a tablet in which drug is embedded in a matrix core of the retardant. So, togetherly the combined inclusion complxation and matrix techniques in a formulation can produces satisfactory results.

Nicardipine [6] is O_5-methyl O_3-[2-(methyl-(phenyl methyl) amino) ethyl] 2,6-dimethyl (3-nitrophenyl)-1,4-dihydropyridine-3,5-dicarboxylate and a dihydropyridine calcium-channel blocker, is used alone or with an angiotensin-converting enzyme inhibitor, to treat hypertension chronic stable angina pectoris, and Prinzmetal's variant angina. [7].

In the present work, an attempt has been made to develop sustained release matrix tablets using hydrophilic materials [8] (sodium alginate, hydroxy propyl methyl cellulose (HPMC)) and hydrophobic material (ethyl cellulose (EC)) employing the inclusion complex of Nicardipine HCl.

MATERIALS AND METHODS

Nicardipine hydrochloride was procured from Cipla ltd. Mumbai. HPMC and EC were purchased from Loba chemicals, Mumbai. Beta cyclodextrin, aerosol and sodium alginate were purchased from Merck Ltd, Mumbai, India. All other chemicals used were procured from authorized dealer and were of high analytical grade.

Preparation of β-Cyclodextrin inclusion complexes

Inclusion complex of Nicardipine and β-cyclodextrin[9] was prepared by kneading method in molar ratios of 1:1, 1:3, 1:5, and 1:7. The drug was dissolved in methanol and β-cyclodextrin (β-CD) was dissolved in water separately. The β-CD solution was added to the drug solution and stirred to attain equilibriums. The resulting paste like material was dried to get solid complex.

Drug content estimation

An accurately weighed quantity of kneaded complex equivalent to 25 mg of drug was taken into a 50 ml volumetric flask and dissolved in minimum amount of methanol and the volume was made up to the mark with 0.1N HCl and the drug content was estimated by using Shimadzu 160A UV/Vis. Spectrophotometer at 238 nm.

In-vitro dissolution study

The in vitro drug release study was carried out for pure nicardipine inclusion complex by using USP XXX paddle type dissolution apparatus at (37 ± 0.5)^{0}C at 50 rpm, in 900 ml of 0.1 N HCl as dissolution media[10, 11]. The drug and inclusion complexes were filled in hard gelatin capsules, such that each capsule contains an equivalent of 25 mg of pure nicardipine. At various time intervals, 5 ml of sample was withdrawn from a fixed position of the vessel and replaced with fresh dissolution medium. The absorbance of filtered sample was recorded at 238 nm. The drug released at various time intervals was calculated.

Preparation of SR matrix tablet

Matrix tablets were prepared by compressing hydrophilic polymer (HPMC K4M), sodium alginate and hydrophobic polymer (Ethyl cellulose) with dispersed drug. All the ingredients along with drug were weighed according to the formula (Table 3)and mixed well in a polythene bag for 15mins.Then the mixture was passed through 40 mesh screen and further mixed with magnesium stearate for 4mins for the purpose of lubrication. The resulting mixture was fed in to the die of 10-station tablet punch machine (Rimek Minipress-I, India) and tablets were prepared using biconcave punches of 8 mm diameter.

Evaluation of powders

Angle of repose

The angle of repose was measured using the funnel method, which indicates the flow properties of powders. The angle of repose was calculated using the following equation.

$$\theta = \tan^{-1} h/r$$

Where, θ = angle of repose, h and r are the height and radius of powder cone.

Density measurement

The Bulk density and tapped density of the drug were determined by pouring gently 2gm of drug sample through a glass funnel into a 10ml clean dry graduated measuring cylinder. The volumes occupied by the sample were recorded. The Bulk density and tapped density were calculated

Bulk density (g/ml) =Weight of the sample in gm/ Volume occupied by sample

Tapped density (g/ml) = Weight of the sample in gm/Volume occupied by the sample after tapping.

Percentage compressibility

It is also one of the simple methods to evaluate flow property of a powder by comparing the bulk density and tapped density. An useful empirical guide is given by Carr's compressibility.

Carr's index= (Tapped density-Bulk density) / Tapped density × 100

Table 1: Drug content estimation of prepared complexes

Drug:ß-CD ratio	Percentage of drug content
1:1	98.134±0.002
1:2	95.637±0.023
1:3	97.428±0.031
1:5	96.221±0.045

Table 2: *In-vitro* dissolution profiles of kneaded complexes

Time (min.)	Cumulative percentage pure drug release	Cumulative percentage drug release from kneaded complex			
		1:1	1:2	1:3	1:5
0	0	0	0	0	0
15	28.212	84.406	74.162	72.048	73.217
30	35.263	85.056	79.528	80.666	80.228
45	41.125	89.934	82.617	82.617	81.568
60	48.287	92.211	90.422	83.105	84.764
75	55.369	94.652	93.467	83.595	83.229
90	62.182	96.113	94.487	88.786	85.129
105	66.224	99.652	97.902	90.422	87.613
120	69.358	-	98.227	93.127	91.228
150	72.251	-	98.614	97.283	92.227

Evaluation of tablets

Weight variation

Twenty tablets of each batch were weighed; the average weight was calculated and compared with the weight of each tablet. The tolerance in weight variation was allowed according to USP XXVI.

Diameter

The diameter of the tablet can be used as initial controlled parameter. The diameter of 10 each batch were measured using vernier calipers and was tried to control within 5% variation of the standard value.

Hardness test

Ten tablets of each batch were selected and their hardness factors were measured using Pfizer hardness tester. It measures the pressure required to break a diametrically placed matrix tablet.

Friability test

Ten tablets were weighed and placed in the Roche fribilator test apparatus. The tablets were exposed to rolling and repeated shocks, resulting from free falls within the apparatus. After 100 revolutions, the tablets were reweighed. The friability was determined using following formula.

% friability = [1-weight of the tablet after test /weight of the tablet before test] ×100

Drug content estimation

Five tablets were weighed individually and the drug was extracted with 0.1N HCl. Drug content (Nicardipine) was estimated by measuring the samples at 238 nm using Shimadzu 160A UV/Vis. Spectrophotometer

***In-vitro* dissolution study**

The dissolution studies [12] were performed according to the USP XXIII, using rotating paddle method. The dissolution medium (900 ml) consisted of acidic buffer (pH 1.2) for first 2 hrs and phosphate buffer (pH 6.8) for subsequent 3 to 12 hrs.The stirring speed of the paddle was 100 rpm, and the temperature was maintained at 37°C ± 0.5°C. The samples (1 ml) were withdrawn at various time intervals, filtered through whattman filter paper and analyzed by UV-Visible spectrophotometer.

RESULTS AND DISCUSSION

Solid inclusion complexes of nicardipine and β-CD were prepared in different molar ratios (1:1, 1:2, 1:3, 1:5) by kneading method. The percentages drug contents of all prepared complexes were calculated and shown in table 1. The Result indicated that 1:1 molar ratio complex has higher dug content of about 98%.Dissolution profiles of pure nicardipine and nicardipine β-CD inclusion complexes were determined. The data on cumulative percentages drug release is presented in Table-2 .The comparative dissolution profile of all complexes and pure drug were analyzed. It can be seen that after 15 minutes only 28 % pure drug is dissolved and even after 60 minutes only 48 % drug goes into solution where as in case of nicardipine and β-CD inclusion complex 84% drug was released with in 15 minutes and almost complete release was observed after 105 minutes. Hence, it can be concluded that inclusion complexes exhibit higher dissolution profile than pure drug as indicated in fig. 1.

Table 3: Composition of different formulations

Ingredients	Quantity of Ingredient / Tablet (mg) Batch Number								
	F1	F2	F3	F4	F5	F6	F7	F8	F9
Nicardipine*	96	96	96	96	96	96	96	96	96
MCC	25	25	25	25	25	25	25	25	25
HPMC(K4M)	50	50	50	50	50	50	50	50	50
Sodium alginate	60	60	65	65	70	70	75	75	80
Ethyl cellulose	-	10	10	-	-	10	10	-	-
Magnesium stearate	2	2	2	2	2	2	2	2	2
Aerosol	2	2	2	2	2	2	2	2	2

The Nicardipine was taken as equivalent weight and symbolized as asterisk (*)

Table 4: Evaluation of blended powders

Formulation No.	Bulk density (X±SD)	Tapped density (X±SD)	Carr's Index %	Hausner's ratio	Angle of repose (X±SD)
PF1	0.436± 0.01	0.501± 0.002	12.97	1.14	30.22± 0.21
PF2	0.489± 0.06	0.493 ± 0.02	10.36	1.008	29.36 ± 0.22
PF3	0.428±0.002	0.512±0.017	16.07	1.19	30.05 ±0.16
PF4	0.465 ± 0.011	0.521 ± 0.021	10.74	1.12	28.42 ±0.18
PF5	0.492 ± 0.015	0.529 ± 0.003	6.99	1.07	30.08± 0.48
PF6	0.433 ±0.012	0.538 ± 0.016	19.51	1.24	32.56± 0.12
PF7	0.482 ±0.003	0.522 ± 0.003	7.66	1.08	30.62± 0.04
PF8	0.421 ± 0.011	0.514± 0.022	18.09	1.22	30.22± 0.28
PF9	0.473 ± 0.002	0.497 ± 0.007	6.82	1.05	28.16 ±0.04

Data are represented as mean ± standard deviation, n=3, Blended powders are represented as PF.

Table 5: Physico chemical properties of prepared tablets

Formulation No.	Avg. Wt. (mg) (X±Sd)	Hardness (kg/cm2) (X±Sd)	Diameter(cm) (X±Sd)	Friability (%)	Drug Content (X±Sd)
F1	236.22± 0.479	5.08±0.322	7.68±0.039	0.013	99.234±0.604
F2	244.83±0.644	6..02±0.289	7.33±0.062	0.025	98.64±0.712
F3	245.12±0.712	7.06±0.365	7.68±0.048	0.011	99.37±.0235
F4	239.28±0.666	7.68±0.441	7.92±0.038	0.026	97.579±0.413
F5	243.28±0.764	6.88±0.284	7.72±0.048	0.018	99.885±0.524
F6	254.58±0.212	7.28±0.462	7.12±0.041	0.021	99.372±0.228
F7	258.12±0.462	7.66±0.287	7.98±0.037	0.013	99.895±0.463
F8	253.18±0.518	569±0.423	7.79±0.44	0.029	98.79±0.182
F9	258.224±0.341	6.72±0.501	7.96±0.039	0.016	98.23±0.231

Data are represented as mean ± standard deviation, n=3

Table 6: *In vitro* drug release pattern of different formulations

Sl no.	Time (hrs)	F1	F2	F3	F4	F5	F6	F7	F8	F9
1	0	0	0	0	0	0	0	0	0	0
2	0.5	18.01	6.81	6.92	7.09	7.227	8.008	8.12	4.52	14.34
3	1	28.90	21.22	11.32	18.10	21.33	24.16	20.16	9.40	27.12
4	2	44.82	36.34	22.95	28.62	34.33	33.34	34.13	21.22	39.11
5	3	55.26	56.64	40.22	41.22	46.18	51.41	41.41	28.36	50.23
6	4	59.73	68.68	49.45	48.57	57.61	64.18	54.25	35.22	57.13
7	5	68.58	75.20	62.28	55.20	64.16	70.11	61.66	45.22	64.63
8	6	72.56	81.23	77.46	66.70	74.82	81.28	68.82	51.21	73.12
9	7	77.95	88.26	88.60	74.18	84.73	88.52	72.24	64.89	80.72
10	8	92.01	90.56	94.24	89.22	94.33	99.27	79.23	80.19	84.73
11	9	96.02	95.35	98.51	99.28	99.73	99.29	81.19	98.28	99.29
12	10	97.22	99.60	99.28	99.72	-	-	89.56	99.12	-
13	11	97.82	-	-	-	-	-	99.32	-	-

All the data represents cumulative percentage drug release from each formulation

Table 7: Regression analysis of different release kinetics of formulations

Formulations.	Zero-order	First-order	Higuchi	Korsemey-Peppas	Release exponent (n) values
F1	0.9845	0.8808	0.9915	0.9844	0.988
F2	0.9305	0.8409	0.9611	0.9327	0.965
F3	0.9428	0.9273	0.9733	0.9846	0.984
F4	0.9628	0.7626	0.9909	0.9901	0.993
F5	0.9909	0.7913	0.9801	0.9769	0.996
F6	0.9796	0.8213	0.9620	0.9529	0.987
F7	0.9691	0.7126	0.9944	0.9629	0.993
F8	0.8743	0.7334	0.9895	0.9889	0.988
F9	0.9632	0.6709	0.9731	0.9947	0.994

Matrix tablets of complexed Nicardipine were prepared by direct compression technology using various polymers. A total of 9 formulations were prepared with varying concentrations of polymer blends. The formulations were evaluated for various quality control tests. All the formulations were found to be satisfactory and reproducible as observed from the data in Table-4.Tablet hardness was found to be good (between 5-7 kg/cm^2) and friability was less than 0.5 % as observed in Table-5.

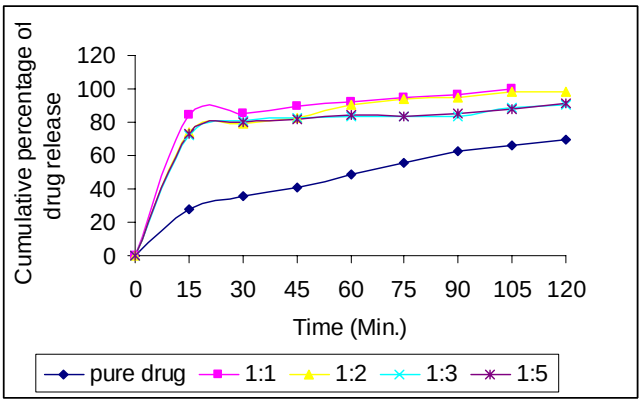

Fig. 1: *In-vitro* drug release from prepared complexes.

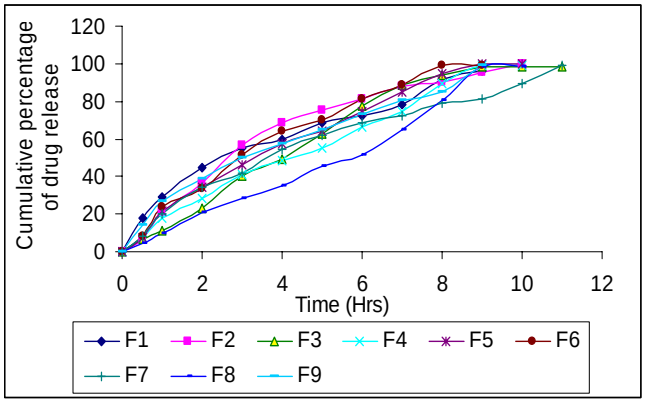

Fig. 2: Dissolution profiles of various tablet formulations.

All the formulations contained sodium alginate in increased concentration ranging from 25%-30%. As shown in fig-2, the formulation F1 with 25% sodium alginate showed 18 % release at 0.5 hrs and 92% drug release at 8 hr of dissolution study. However, formulation F2 containing same percentage of sodium alginate showed only 6% drug release at first half an hour. Sudden release of drug from formulation F1 could be due to sudden bursting of tablet. As all formulations contained increased in concentrations of sodium alginate, simultaneously they retard the release of drugs for prolonged period of time. A comparison was done between formulation F3 and F4 containing 26% and 27% of sodium alginate, but formulation F3 retarded the drug release for a prolonged period of time. This could be due to presence of ethyl cellulose that acts as hydrophobic diffusional barrier. Formulations F5 and F6 containing 28% and 27% of sodium alginate released 74%and 81% of drug with in 8hr of dissolution study. Therefore, from the above study it is cleared that drug-retarding property proportionally increased due to hydrophilic matrix forming agent (sodium alginate), with that ethyl cellulose plays a major role in retarding property. Tablets of formulation F7 have shown better drug retarding ability upto 12 hr that shows that 28% of sodium alginate is the minimum quantity required to retard the release of nicardipine from matrix tablet. The

in-vitro release pattern of the optimized formulation was analyzed by fitting the dissolution data into various kinetic models. It was seen that R^2 value was higher when fitted to Higuchi model, (table 7) followed by zero order equation. This indicated a Higuchi release from the optimized nicardipine matrix tablets.

CONCLUSION

It can be concluded that 1:1molar ratio complex showed maximum dissolution pattern and suitable combination ratios of hydrophilic and hydrophobic polymers [13] will retard and prolong the drug release. Further *in-vivo* study has to be carried out to check the efficacy of preparations.

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