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Original Article

Formulation, release and stability study of Bupropion sustained release 150 mg using Hydroxypropylmethylcellulose (HPMC) 4000cps basis

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Abstract

In this study,formulation of sustained-releasingmatrix tablet of bupropion 150 mg, usinghydroxypropylmethylcellulose(HPMC) 4000cps was evaluatedwith the aim of reducing the frequency of daily dose. The level of HPMC4000 ,polyvinylpyrolidone(PVP) and magnesium stearate(Mg St)was varied based on a 2level 3 factor factorial experimental designusing the release rate of the drug from the matrices as the response variable. Themechanism of drug release from hydrophilic matrix tablets is complicated but it is known to be related to dissolution of drug and its diffusion through the hydrated portion of matrix and erosion of the outer hydrated polymer on the matrix surface.Granules of the optimum formulations were compressed into tablets using EK-O lorsch single punch tablet machine. Evaluation of tablets including weight variation,crushing strength and friability demonstrated acceptable results.Based on dissolution data of the eight tablet formulations resulted from the experimental design, a polynomial regression equation was generated and used for obtaining the optimum formulations.Invitro dissolution tests also revealed sustained release of drug for an 8 hours period at the end of which almost complete release was achieved. According to release studies formulation A,AB and C has been selected for long term stability studies.

Key words: Controled release, Bupropion, Hydroxypropylmethylcellulose

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1. Introduction

The hydrophilic matrix tablets designed with water soluble polymers are extensively used in control release development. Among hydrophilic polymers,hydroxypropyl methylcellulose or HPMC is the most widely used excipient due to its distinct advantages: the polymer has an excellent safety record; its non-ionic nature leads to minimization of the interaction problems in acidic, basic, or other electrolytic systems; availability of the polymer in a wide range of viscosity allows for developing different coating formulations and the subsequence screening the most effective ones (Sandi P B. Tiwari, et al; 2008) and finally the data for development studies is abundant. Evidences suggest that HPMC with 4000 cps viscosity is suitable for slowing down drug release especially in shorter period of time (RunnaRao Ravi et al; 2007 and SanatuGhosh et al 2010).

In this study HPMC 4000 was used as sustain release agent for once-daily Bupropion extended-release dosage form. Bupropion is a dopamine –reuptake inhibitor which is used as an antidepressant and prescribed for smoking cessation. The drug however is subjected to some disadvantages including the short biological half-life and high dosing frequency. Studies identified a relationship between peak plasma concentration of bupropion and some adverse effects like epilepsy. These problems render use of the bupropion immediate form inconvenient for patients, and the drug as an important candidate for sustained release development.

Herein we present the report of preparing a suitable extended-release formulation Bupropion. The effect of some factors, such as the concentration of Magneseium Stearate (Mg St) and polyvinyl pyrolidone (PVP) as well as the concentration of polymer on drug release was investigated by utilizing the 23 factorial designs and the best of formulations were chosen for long term stability studies.

2. Materials and Methods

Materials

The following reagents were used:Bupropion hydrochloride(Supor,India), lactose monohydrate, Microcrystalline cellulose (Avicel), hydroxyl propylmethylcellulose (HPMC), magnesium stearate(Mg St) andpolyvinylpyrolidonewere gifts from Hakim pharmaceutical company.

Equipment

Single punch tablet machine(Lorsch,Germany), U.V.spectrophotometer(Cecil ,England), hardness tester (Dr.schleunigerpharmaton 5y,USA),friabilator (Dr.schleunigerpharmaton FR1000,USA), dissolution tester(Erweka DT60, Germany)

Methods

Factorial design experiment:

Tablets were obtained based on the 23 factorial designprocedure: HPMC concentrationX1; PVP concentration X2; and Mg St concentration X3 were selected as independent variables(table 1) and the effect of these

Table 1: Factors used in the factorial design experiment

Factor	Low level	High level
Hydroxypropylmethylcellulose(%) (X1)	10	15
PVP(%) (X2)	3	5
Magnesium stearate (%) (X3)	1	1.5

variables on drug release was also investigated. The compositions of all model formulation are summarized in (table 2). The percentage of drugrelease at 1,4,8 were selected(according to

Table 2: Compositions of the model formulations

Formulation The formulations(%/tab)	1	A	B	C	AB	AC	BC	ABC	Function of each agent
Bupropion Hydrrochloride	60	60	60	60	60	60	60	60	Active Ingredient
HPMC 4000cps	10	15	10	10	15	15	10	15	Retarding Agent
PVPk30	3	5	3	3	5	3	5	5	Binder
AvicelPH102	10	10	10	10	10	10	10	10	Filler
Lactose Monohydrate	16	11	14	15.5	9	10.5	13.5	18.5	Filler
Mg St	1	1	1	1.5	1	1.5	1.5	1.5	Lubricant
Ethanol 96º	0.064	0.064	0.064	0.064	0.064	0.064	0.064	0.064	Solvent for binder

the USP 33) asresponse variables to detect the profile and ensurecomplete drug release.

Tablet preparation:

The drug and excipients were weighed and mixed well. PVP was dissolved in 96º alcoholand then the solution was added to make a wet mass. Afterwards the wetcomponent was passed through a 14 mesh sieve. Thegranules were dried in roomtemperature for 24 hours, and thenblended with 1% or 1.5%(dependents on formulation) of magnesium stearate. Tablets containing150mg of bupropion were compressed using 9 mmdiameter incavated-punches. The upper punch compactionpressure applied was 8-15 kps.

Evaluation of tablets:

Tablets were subjected to various physical tests which include weight variation, thickness, hardness, friabilityand dissolution testing. For hardness and weight testing, ten randomly chosen tabletswere examined from each set. The tablet friability testing was performedon a friabilator. The 10 tablet sampleswere tumbled for 4 min. Afterwards,the percent weight loss was calculated.

Determination of the release of bupropion from HPMC 4000cps matrix tablet:

The United States Pharmacopoeia (33) paddle method was used for all in vitro dissolution studies. Water was used as a dissolution medium. The rate of stirring was 50 rpm. The bupropion tablets wereplaced in 900 ml of water and maintained at 37º. Five milliliters of samples were taken at appropriateintervals(1,4,8hrs according to the

USP 33). The samples were analyzed by UV spectrophotometry at 298 nm. At least 3tablets of each formulation were used. The mean andstandard deviation ofpercentage dissolved were calculated.

Long term stability studie:

Three formulations (A,AB and C) were chosen for long term stability studies whichwere performed according to the ICH'sguideline (tempruture:25°±2 and moisture: 60%±5). The drug release ofthese three formulated tablets was studiedduring 1,3 and 6months.

3. Result and discussion

Tablets were readily compressed with no change required in the ratio of excipient. The pressed tablets were smooth, shiny and can be applieddirectly or aqueous polymer coating (for patient more compliance and palatability) in experimental administration Weight variation was within limit of ±5%.

Table 3: Physical and chemical parameters of formulated bupropion tablets

factor / formulation	thickness (mm) n=10	Weight(mg) N=10	Hardness(kp) n=10	(%) friability n=10
1	4.3±0.01	250.2±3.48	9.7 ± 1.02	0.40
A	4.3±0.01	252.3±2.82	11.8±1.22	0.50
B	4.3±0.02	251.4±2.35	11.7±1.71	0.40
C	4.2±0.01	250.7±2.14	11.7±1.48	0.10
AB	4.1±0.01	250.3±2.10	13.5±1.75	0.30
AC	4.2±0.01	249.1±1.58	11.5±0.93	0.52
BC	4.2±0.01	251.9±1.67	9.7±0.91	0.40
ABC	4.2±0.01	250.9±2.15	10.6±1.51	0.56

The hardness was set at 8 to15 kps. Table 3 represents the actual values.Thickness was set at a range of 4.2 mm ±5%.
Mean drug content valueobtained by assay procedure was within the USP's range(90% to 110%).
The dissolution profiles and the responses of all model formulations required by the

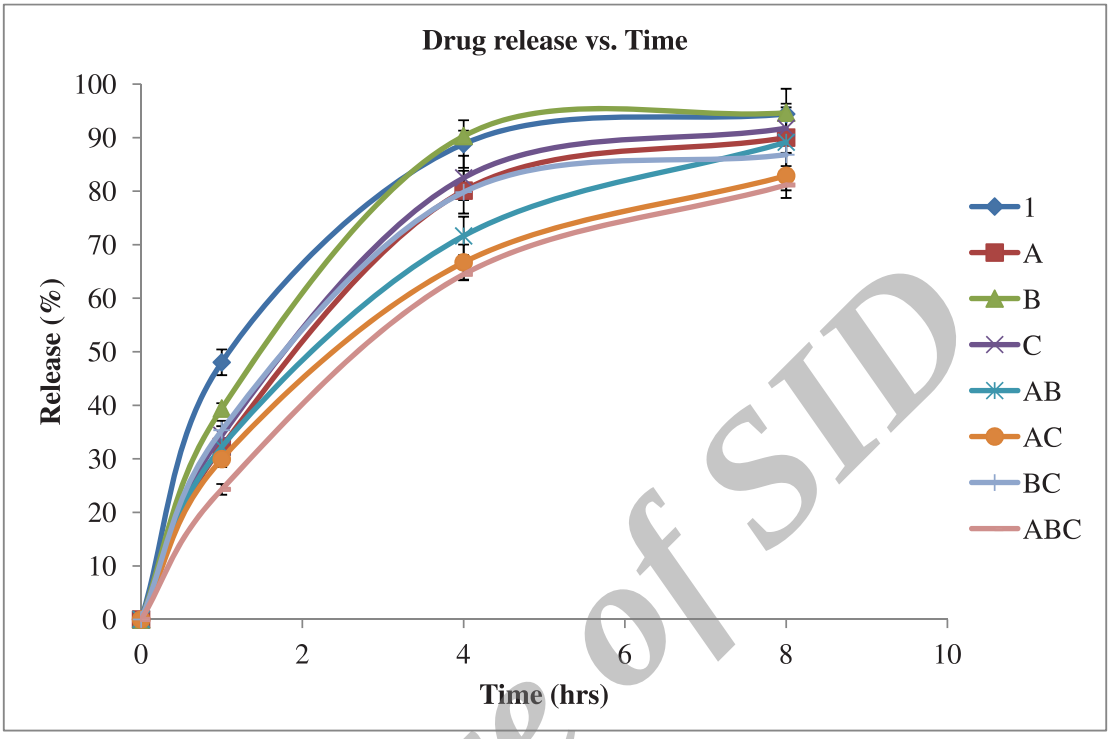

Figure 1: Drug release profile of Bupropion in different formulations of sustained release tablets

factorial design are given inFig.1 and Table 4 respectively. The wide variation indicates-the different drug release rates as a result ofcombinatorial factoreffetcs.
Table 4 indicates that variables at low compare to high levels show significant changes in drug release. In formulation 1 which all variables are at low level drug release is higher than the range defined by USP 33. On the other hand, in formulation ABC which all variables are at high level drug release is lower than USP range. So it can be concluded that the selected

Table 4: Drug release from different formulations in defined intervals

Release (%) / Time(hr)	1	A	B	C	AB	AC	BC	ABC
1	48.3±0.66	32.2±0.78	39.4±0.71	34.4±0.81	32.2±0.72	29.9±0.65	35.3±2.7	24.3± 0.66
4	88.8±0.67	80.1±0.75	90.3±0.73	82.5±0.77	71.6±0.75	66.6±0.70	79.8±0.3	64.4± 0.70
8	94.4±0.7	90.0±0.77	94.6±0.77	91.7±0.79	89.1±0.7	82.8±0.68	86.8±1.4	81.1± 0.69

range is a suitable range and by evaluating these result a formulation with suitable physical and chemical features as well as drug release can be selected.

By reviewing the drug profile, it can be explained that the rate of drug release as well as the burst effectdecreased with an increase in the tablet content of HPMC4000 cps. Moreover drug release in formulation A(with HPMC at high level) is lower than drug release in formulations 1, B and C suggesting that at high levels of HPMC the release of drug will be reduce significantly comparing to Mg St and PVP.

For the controlled release under investigation, which is a matrix-tablet comprising drug, and hydrophilic polymer(HPMC),the release should follow three steps.

First the dissolution medium ispenetrated in the tablet matrix (hydration). Then the matrix is swelled with concomitant ordissolved. The dissolved drug isfinally transported either through the hydrated matrix or from theparts of the eroded tablet, to the surrounding dissolution medium(Kiortsis, Kachrimanis et al. 2005).

Theobtained release profiles, suggest that high levels ofPVPhas small affecton reduction of drug release. The drug release of the formulation B is almost similar to that offormulation 1. Although the release profile in formulation B is marginally lower than formulation 1. Therefore,PVP in high concentration could have positive effect on reduction of drug release. This is perhaps due to an increase in bonds and reduction ofwater penetration into system, consequently water absorption by HPMC polymer and creategel layer will decrease, that could inhibit drug release. Comparison of (what of) formulations (B)(with high level of PVP) and C (high level of Mg St), shows that Mg St has stronger effect on decreases drug release relative to PVPwhich can be explained by the hydrophobic nature of Mg St: once the tablet is exposed to water or gastro intestinal fluid, less water may enter to the tablet and absorbed by HPMCpolymer resulting in a decrease matrix swelling and a slow drug release.

By studying the profile, it is revealed that even though high levels of PVP cannot have significant effect on drug release but sufficiently high levels of both PVP and Mg St (corresponding to formulation BC)may cause a slowdown in the release of the drug. As a result PVP at high level and Mg St at high level could prevent waterpenetration and delay the formation of a gellayer by HPMC polymer and the swelling mechanism to furtherslow down the drug release.By comparing formulation BC(PVP and Mg St at high level)with formulation AB (PVP and HPMC at high level) it can be concluded that PVP and HPMC at high level is more effective in alleviation of the drug release comparing to PVP and Mg St at high level. This indicates that HPMC is the main factor insustain releasing the drug.

Also when Mg St and HPMC at high level are used, drug release shows more reduction compared to PVP and HPMC at high levels. This confirm that Mg St has a greater effect on sustain releasing the drug in comparison to PVP.

The drug release of the three formulations 1,ABC and B is out of the range defined by USP 33,therefore,they were rejected. Among the five remaining formulations, although the drug release in formulations BC and AC were in the USP defined range, less drug was released especially at the last time (after eight hours). Although the reduction of drug release was the main goal in this study but sufficient drug has to be released in predetermined time comparable to the gastrointestinal residence time. Therefore the formulations were not selected for stability studies and instead the three formulations(A),(AB) and (C) which release appropriate amount of drug were used for further stability studies.

In long term stability studies,none of the formulated tablets showed anychange of color, smell or physical appearance. Moreover the release of drugs in all three formulated drugs

Table 5: Drug release studies after 6 month of long term stability

Release(%) / Time(hr)	A	AB	C
0	0	0	0
1	33.51±0.66	31.90±0.70	34.23±0.58
4	81.76±0.62	77.92±0.68	83.37±0.60
8	99.71±0.69	98.01±0.67	102. 0±0.55

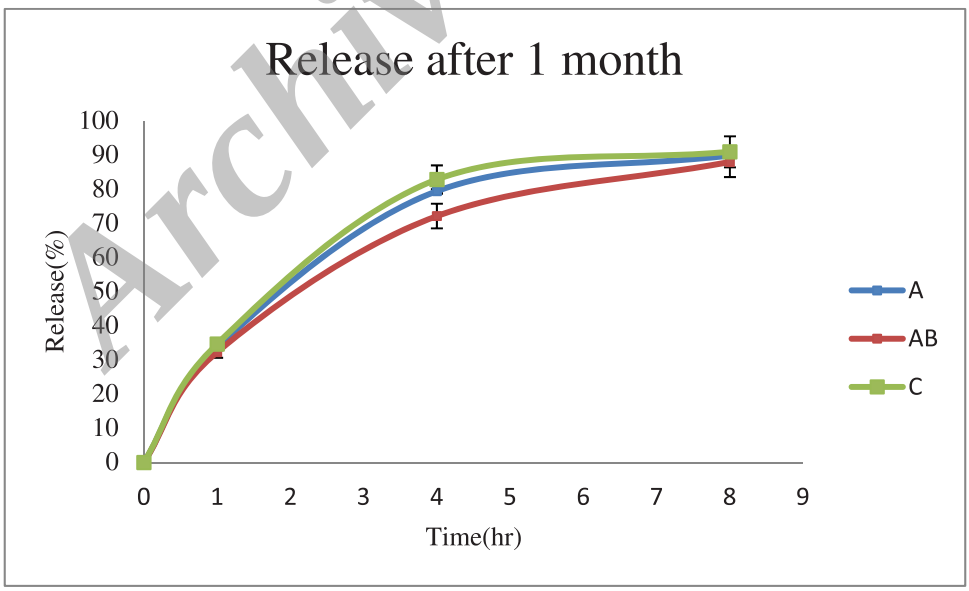

Figure 2: Drug release profile of Bupropion sustained release tablets after 1 month

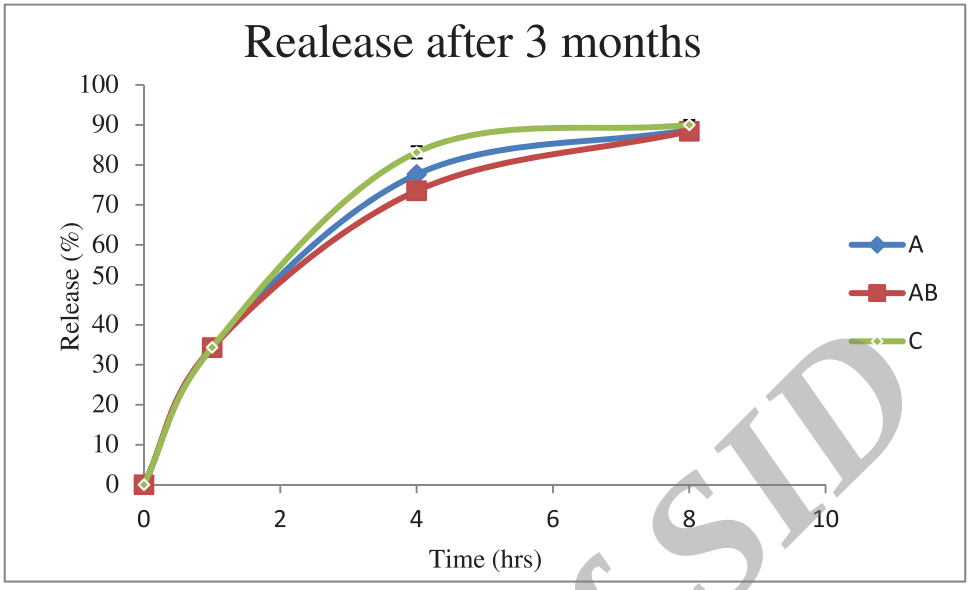

Figure 3. Drug release profile of Bupropion sustained release tablets after 3 month

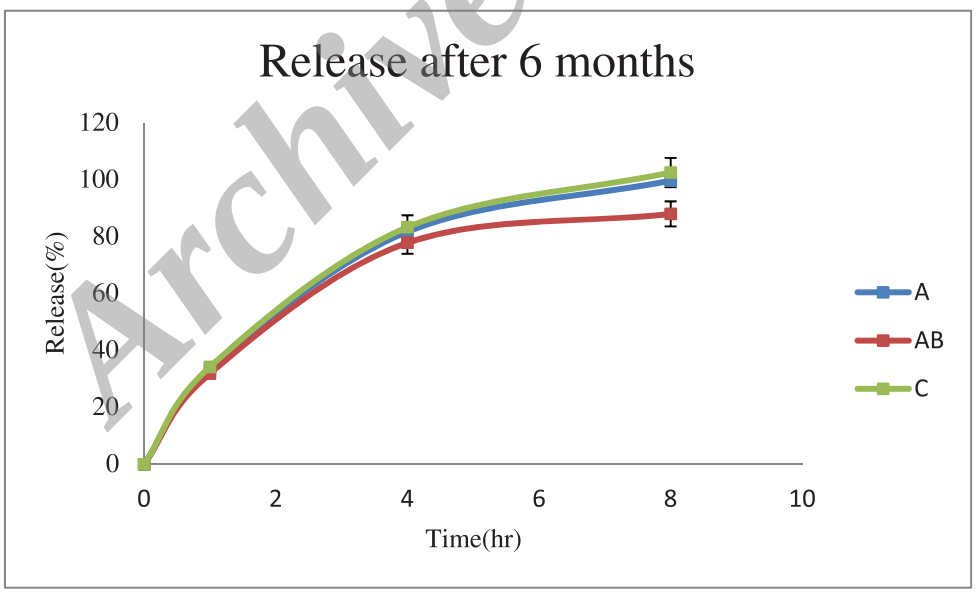

Figure 4: Drug release profile of Bupropion sustained release tablets after 6 months

in months 1,3 and 6 were validated according to the USP 33 instruction

4. Conclusion

Bupropion sustained release matrix tablet was preparedsuccessfully using HPMC 4000cps polymer by a 23 factorial design to retard the drug release andachieve an optimum dissolution profile. The results of this study showed that HPMC was the main determining factor. Also Mg St had more effect on sustain releasing the tablet than PVP.

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Conflict of interests : None declared.

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