Development and \textit{in vitro} characteristics of bupropion HCl sustained release matrix tablets one


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Abstract
An attempt was to develop the oral sustained release Bupropion hydrochloride matrix tablets by using HPMC K100, Carbopol, and Eudragit by direct compression method. The \textit{in-vitro} characteristics the blends of different formulations were evaluated for pre-compression evaluations (angle of repose, bulk density, tapped density, Carr’s index, Hausner’s ratio). Its shows satisfactory results. The tablets were subjected to friability, weight variation, thickness, hardness drug content, and \textit{in-vitro} release studies. The \textit{in-vitro} dissolution study was carried out for 12 hrs using USP dissolution apparatus II (paddle) in 900ml 0.01 HCl solution as dissolution media. The amount of drug released was determined at 280 nm by UV-visible spectrophotometer. From the results F6 was found to be 99.21% release 12 hrs and finalized as optimized formula. The release mechanisms of F6 formulation were explored and it follows Zero order release and Korsmeyer’s peppas $n$ value was found to be 0.148, it shows that combined mechanisms like diffusion through the matrix and partially through water-filled pores. It is cleared that the drug released from matrix tablets prepared by Eudragit provides a better release result in preparation of SR formulation of bupropion hydrochloride.

Key words: Bupropion Hydrochloride, Sustained Release, Matrix Tablets.

INTRODUCTION
Sustained release dosage forms
The sustained drug action with oral dosage form is achieved by affecting the rate at which the drug is released from the dosage form and/by slowing the transit time of dosage form through the gastro intestinal tract [1-3]. The rate of release from these system is obtained is as follows. Sustained release, sustained action, prolonged action, controlled action, extended action and timed release are terms to identify drug delivery system that are designed to achieve a prolonged therapeutic effect by continuously releasing medication over an extended period of time after administration of a single dose. Simply sustained release is defined as any drug or dosage form modification that prolongs the therapeutic effect. Modifying drug dissolution by controlling access of biological fluids to the drug through the use of barrier coating. Controlling drug diffusion rates from dosage forms [4]. Chemically reacting or interacting between the drug substance and its pharmaceutical barrier and site specific biological fluids. The advantages of sustained release dosage forms were control of drug therapy is achieved the rate and extent of drug absorption can be modified, frequency of drug administration is reduced, Patient compliance can be improved, Drug administered can be made convenient, maximum the availability of drug with minimum dose, the safety margin of high potency drug can be increased [5-6].

The present study was to develop Bupropion Hcl sustained release matrix tablets by maintaining the concentration of administered drug within therapeutically effective range thereby decreasing the dosing intervals. Bupropion is an anti depressant used for smoking cessation and to treat a variety of conditions, including depression and other mental/mood disorders. Antidepressants can help prevent suicidal thoughts/ attempts and provide other important benefits [7].

MATERIALS & METHODS
Materials
Bupropion Hcl is obtained from Lara drugs Pvt. Ltd,
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HPMC K100, Carbopol (Lara drugs Pvt Ltd, Hyderabad), Eudragit (Brahmar Cellulose Pvt Ltd– Cuddalore), Micro crystalline cellulose (Lara drugs Pvt Ltd, Hyderabad), Mg.stearate, Talc(S.D Fine chemicals, Mumbai).

METHODS

STANDARD CURVE OF BUPROPION HCl
Preparation of Bupropion HCl standard stock solution
A standard stock solution of Bupropion HCl was prepared by dissolving accurately weighed 150mg of Bupropion HCl with a little quantity of phosphate buffer solution, in a 100ml volumetric flask. The volume was made up to 100ml by using 0.01N HCl solution, to obtain stock solution 1000µg/ml. From the above stock solution several dilutions were made to obtain 50, 75, 100, 125, and 150 mcg/ml. Finally the absorbance of dilutions was measured at 280nm.

INCOMPATIBILITY STUDIES
Physical Incompatibility Studies
The active ingredients and the excipients were mixed in the selected ratios using a mortar and pestle. The mixtures were transferred into glass vials and sealed. The samples were placed as first set of initial samples and second set of samples were kept at 40° ± 2°C / 75% ± 5% RH for 4 weeks. The samples were analyzed for physical parameters.

CHEMICAL INCOMPATIBILITY STUDIES
FTIR (Fourier transform infra-red spectroscopy) studies
Compatibility study of drug with the excipients was determined by using FTIR. The sample powder of drugs, excipients and mixture of both were subjected to FTIR study. The mixture spectra were compared with that of the original spectra.

COMPRESSION EVALUATION PARAMETERS

Table 1. Formulation development of Bupropion HCl Matrix tablets

<table>
<thead>
<tr>
<th>Excipient</th>
<th>F1</th>
<th>F2</th>
<th>F3</th>
<th>F4</th>
<th>F5</th>
<th>F6</th>
</tr>
</thead>
<tbody>
<tr>
<td>API</td>
<td>150</td>
<td>150</td>
<td>150</td>
<td>150</td>
<td>150</td>
<td>150</td>
</tr>
<tr>
<td>HPMC K100</td>
<td>100</td>
<td>150</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Carbopol</td>
<td>-</td>
<td>-</td>
<td>150</td>
<td>100</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Eudragit</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>100</td>
<td>150</td>
</tr>
<tr>
<td>MCC</td>
<td>142</td>
<td>92</td>
<td>92</td>
<td>142</td>
<td>142</td>
<td>92</td>
</tr>
<tr>
<td>Magnesium state</td>
<td>4</td>
<td>4</td>
<td>4</td>
<td>4</td>
<td>4</td>
<td>4</td>
</tr>
<tr>
<td>Talc</td>
<td>4</td>
<td>4</td>
<td>4</td>
<td>4</td>
<td>4</td>
<td>4</td>
</tr>
</tbody>
</table>

Bulk density
The bulk density (g/ml) depends on particle size distribution. Accurately weighed powder was to measuring cylinder through large funnel and volume was measured, in initial bulk volume [6-8].

\[
D_b = \frac{M}{V_0}
\]

Where, M is the mass of powder.
V_0 is the bulk volume of the powder

Tapped Density
The powder was introduced into a dry 100 ml measuring cylinder. The cylinder was then tapped 100 times from a constant height and the tapped volume was read. It is expressed in gm/ml.

\[
D_t = \frac{M}{V_t}
\]

Where, M is the mass of powder.
Vt is the tapped volume of the powder

Angle of Repose
Funnel was mounted on a stand at a fixed height and a fix weighed quantity of each blend was poured through the funnel. The 52 height and the base diameter of the pile was noted and calculated as (h/r).

\[
\text{Angle of repose} = \arctan\left(\frac{h}{r}\right)
\]

Where, h and r the height and radius of the powder cone.

Formulation development of sustained release matrix tablets
The active ingredient i.e. Bupropion HCl and each three types of polymers (HPMC K100 and Carbopol and Eudragit) Filler MCC, lubricant (magnesium stearate) and glidant (talc) were blended together by dry mixing in a laboratory mixer (polybags) for 10 minutes. Finally the mixture was compressed by using 12mm standard punch and dies set at compression force 4-5kg.
**POST COMPRESSION EVALUATION PARAMETERS**

**Weight variation**
20 tablets were weighed individually and the average weight was calculated. The requirements if the weights of not more than 2 tablets differ by more than the percentage and on tablets differ in weight by more than double that percentage [9].

Average Weight = \frac{\text{weight of 20 tablets}}{20} \times 100

**Hardness**
Five tablets from each batch were selected and hardness was measured using Monsanto hardness tester to find the average tablet hardness.

**Friability**
The friability was measured by using in lab equipments, Madras. Friability was evaluated from the 20 tablets was friabilator at 25 rpm for 4 minutes in 100 rotations. Tablets were removed and weighed in calculated the (%).

\%F = \frac{1}{\text{loss in weight/ initial weight}} \times 100

**Content uniformity**
At random 10 tablets are weighed and powdered. The powder equivalent to 150mg was weighed accurately and dissolved in 100ml of 0.01 HCl solution. The solution was shaken thoroughly. The un-dissolved matter was removed by filtration through Whatman No.1 filter paper. Then transfer 1ml of the above solution into a 100ml volumetric flask and make up the volume with 0.01N HCl solution. The absorbance of the diluted solution is measured at 280nm by using UV spectrophotometer.

**In-vitro Dissolution studies**
The in vitro dissolution drug release study was performed for all the tablets using USP II dissolution apparatus at 50 rpm using 900 ml of 0.01N HCl dissolution medium. Temperature of the dissolution medium was maintained at 37±0.5°C, the dissolution sampling volume was 5ml and sampling time intervals for 2, 4, 6, 8, 10, 12 hours. The absorbance of filtered solution was checked by UV spectrophotometric method at 280 nm and dissolution rate was studied for all developed formulations.

**In-vitro release mechanism of sustained release systems**
The in-vitro release mechanism has been performed for the matrix tablets. Depending upon R² and slope values obtained from different models. The best fit model was selected [10].

**Zero order release**
Drug dissolution from dosage forms that do not disaggregate and release the drug slowly can be repeated as

\[ Q = Q_o + K_o t \]

Where Q is the amount of drug release or dissolved (assuming that release occurs rapidly after the drug dissolves) Q_o is the initial amount of drug in solution (it is usually zero) and K_o is the zero order release constant. The plot is made, cumulative percentage drug release \( v \) time (zero-order kinetic model). Zero order release is mainly applicable to dosage forms like transdermal system, osmotic system, matrix tablets with low soluble drugs.

**First order release**
The first order release rate kinetics the release data were fitted into the following equation.

\[ \log C = \log C_0 - K_1 t / 2.303 \]

Where c is the amount of drug released at time t, C_0 is the amount of drug in the solution and K_1 is the first order release constant.

This model is applicable to study of hydrolysis kinetics and to study the release profiles of pharmaceutical dosage forms such as those containing water soluble drugs in porous matrices.

**Higuchi Model**
This model is based on the hypothesis that Initial drug concentration is much higher than drug solubility. Drug diffusion takes place only in one dimension (edge effect must be negligible. Drug molecules are much smaller than system thickness. Matrix swelling and dissolution are negligible. Drug diffusivity is constant. Perfect sink conditions are always attained in the release environment. Higuchi describes that the release of drugs from insoluble matrix as a square root of time dependent process based on Fickian diffusion.

\[ Q = K t^{1/2} \]

Where K, is the rate constant reflecting the design variables of the system. This model is applicable to system with drug dispersed in uniform swell- able polymer matrix tablets with water soluble drug.
Korsmeyer-Peppas Model
Korsmeyer (1983) derived a simple relationship which describes the drug release from a polymeric system. To find out the mechanism of drug release, first 60% drug release data was fitted in Korsmeyer-peppas model.

\[ \frac{M_t}{M_{\infty}} = K t^n \]

Where \( \frac{M_t}{M_{\infty}} \) is fraction of drug release at time \( t \), \( K \) is the rate constant and \( n \) is the release exponent. The \( n \) value is used to characterize different release mechanisms as given in following table for cylindrical shaped matrices.

Stability studies
The optimized formulation (F6) was packed in 0.04mm thick aluminium foil strips laminated with PVC. The packed tablets were placed in stability chamber maintained at 40±2°C and 75±5% RH for 1 month. The samples were withdrawn after one month and were observed for changes on the physical parameter (i.e. change in colour, appearance of spot, any kind of microbial or fungal growth, any bad odour, smoothness). Samples were evaluated for drug content and in-vitro drug release.

RESULTS
Fig 1. Standard calibration curve of Bupropion HCl in 0.01N HCl

![Calibration curve Bupropion HCl](image1)

COMPATIBILITY STUDIES
Drug excipient compatibility studies
The drug and excipient mixtures are evaluated for chemical compatibility by means of FTIR and the results for best formulation are given in the following figure.

Fig 2. Compatibility study of Drug and Excipients
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Table 2. Evaluation of pre-compression parameters

<table>
<thead>
<tr>
<th>Formulation Code</th>
<th>Angle Of Repose (θ)</th>
<th>Bulk Density g/ml</th>
<th>Tapped Density g/ml</th>
<th>Carr’ S Index</th>
<th>Hausner’s Ratio</th>
</tr>
</thead>
<tbody>
<tr>
<td>F1</td>
<td>25°.26 ±0.2</td>
<td>0.401±0.04</td>
<td>0.461±0.06</td>
<td>13.33±0.2</td>
<td>1.15±0.13</td>
</tr>
<tr>
<td>F2</td>
<td>24°.38 ±0.4</td>
<td>0.479±0.02</td>
<td>0.600±0.02</td>
<td>20.00±0.1</td>
<td>1.25±0.11</td>
</tr>
<tr>
<td>F3</td>
<td>26°.20 ±0.3</td>
<td>0.413±0.01</td>
<td>0.502±0.06</td>
<td>17.24±0.3</td>
<td>1.20±0.08</td>
</tr>
<tr>
<td>F4</td>
<td>25°.02 ±0.5</td>
<td>0.428±0.06</td>
<td>0.500±0.04</td>
<td>14.28±0.2</td>
<td>1.16±0.12</td>
</tr>
<tr>
<td>F5</td>
<td>27°.34 ±0.2</td>
<td>0.444±0.15</td>
<td>0.521±0.04</td>
<td>14.81±0.4</td>
<td>1.17±0.16</td>
</tr>
<tr>
<td>F6</td>
<td>25°.24 ±0.4</td>
<td>0.375±0.012</td>
<td>0.480±0.05</td>
<td>27.87±0.5</td>
<td>1.28±0.09</td>
</tr>
</tbody>
</table>

Table 3. Evaluations of Compressed Tablets of Bupropion HCl

<table>
<thead>
<tr>
<th>Formulation</th>
<th>Weight Variation(mg)</th>
<th>Hardness (kg/cm²)</th>
<th>Thickness (mm)</th>
<th>Friability (%)</th>
<th>Drug Content (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>F1</td>
<td>398±3.5</td>
<td>4.2±0.06</td>
<td>4.0±0.02</td>
<td>0.3±0.06</td>
<td>98</td>
</tr>
<tr>
<td>F2</td>
<td>398±3.5</td>
<td>4.5±0.02</td>
<td>4.1±0.12</td>
<td>0.4±0.1</td>
<td>97</td>
</tr>
<tr>
<td>F3</td>
<td>396±4.0</td>
<td>4.7±0.04</td>
<td>3.7±0.16</td>
<td>0.3±0.8</td>
<td>95</td>
</tr>
<tr>
<td>F4</td>
<td>394±4.0</td>
<td>4.8±0.03</td>
<td>3.6±0.08</td>
<td>0.3±0.7</td>
<td>95</td>
</tr>
<tr>
<td>F5</td>
<td>395±3.0</td>
<td>4.3±0.06</td>
<td>3.9±0.12</td>
<td>0.5±0.1</td>
<td>100</td>
</tr>
<tr>
<td>F6</td>
<td>393±5</td>
<td>4.4±0.05</td>
<td>4.2±0.08</td>
<td>0.3±0.2</td>
<td>100</td>
</tr>
</tbody>
</table>

Stability studies
The ideal formulation F6 was subjected to stability studies for a period of 30 days and the drug release, were compared with that of the initial data and found that there was no significant change in the values indicating a stable formulation.

Fig 3. In vitro % of drug release of Bupropion Hcl (F1-F6)

DISCUSSION
The present study was to formulate and characterized the Bupropion HCl sustained release matrix tablet. Compatibility studies are done for both physical and chemical compatibilities were no incompatibilities are found. The Hausner’s ratios of all the formulations are in the range of 1.15±0.13 to 1.28±0.09 mean while the Compressibility index values are in the range of 13.33± 0.2 to 27.87±0.5 proving the In the study of Bupropion HCl was formulated and evaluated successfully. Angle of repose values were also conforming the same by showing the results in the range of 24°.38±0.4 to 27°34±0.2. Hence we can conclude that the tablet
blend has got good flow properties. Fact that the tablet blend has good flow properties. The weights of all the formulations are in the range of 393±5 to 398±3.5 showing that all the formulations are within the pharmacopoeial limits of weight variation. Friability results of all the formulations were found to be less than 1% and all the formulations passed the test.

F1 and F2 batches were formulated using HPMC K100 as polymer for extended release at varying concentrations of 25% and 37.5% respectively of which formulation F1 released 97.6% at 10hrs and formulation F2 released 83.5% at 12 hrs both results were not satisfactory. F3 and F4 batches were formulated using Carbopol as polymer for extended release at varying concentrations 37.5% and 25% respectively, of which formulation F3 released 74.6% at 12 hrs and formulation F4 released 85.7% at 12 hrs. The results were not satisfactory and also hardness was 4.8±0.8kg/cm$^3$ and 4.7±1.2kg/cm$^3$ respectively. F5 and F6 batches were formulated using Eudragit at varying concentration 25% and 37.5% respectively, in-vitro drug release was 101.2% at 10hrs and 99.21% at 12 hrs. The release mechanisms of F6 formulation were explored and it follows Zero order release and Korsmeyer’s peptas $n$ value was found to be 0.148, it shows that combined mechanisms like diffusion through the matrix and partially through water-filled pores. The formulation F6 was subjected to stability studies for a period of 30 days and the drug release was found there was no significant change in the values indicating a stable formulation.

CONCLUSION
Sustained release dosage form for Bupropion HCl were formulated and evaluated. The drug and excipient compatibility studies were performed by using IR Spectroscopy and found that they were compatible. The results concludes that F6 formulation was the best as it has constant drug release initially 37.5% (Bupropion HCl and Eudragit as key excipients) and at the end of 12hrs 99.21% of the drug released. The stability studies were conducted for optimized formulation (F6) as per ICH guidelines at 40°C±2/75±5% RH for 1 month and no changes were observed. Results of stability studies conclude that F6 formulation was stable.

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REFERENCE