INVESTIGATION OF SUPERFLUITY POTENTIAL OF BCS-II DRUG BY USING SOLVENT SHIFT METHOD

Uditi Handa\textsuperscript{a,b}, Anuj Malik\textsuperscript{b*} and Kumar Guarve\textsuperscript{a}

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ABSTRACT

This research work’s motive was to investigate the superfluity potential of the BCS-II drug (Dextromethorphan HBr) by solvent shift method to evaluate the impact of polymer gain factor on superfluity potential for the enhancement of bioavailability of orally prolonged release. To maintain the superfluity potential, different drug-release retarding polymers were used (HPMC 15cps, xanthan gum, sodium CMC) in a bio-relevant medium. The outcomes of this, reveal that all polymers remarkably enhanced the solubility of dextromethorphan HBr 1.07-2.49 fold when compared to those without polymer. HPMC and xanthan gum both at 0.1 w/V showed excellent precipitation inhibitor’s role at about 10.2-22.1 factor in SIF\textsubscript{sp} and 6.04-6.75 factor in PBS (pH 7.4). Elucidation of these results, show that HPMC (15cps) works on the parachute concept and Xanthan Gum on the glider concept. Hence, the superfluity potential is maintained by the selection of excellent polymers in non-formulated drugs to develop the superfluity formulation.

Keywords: Dextromethorphan HBr, Equilibrium solubility, solvent shift method, superfluity potential, Solution Stability, Degree of supersaturation

INTRODUCTION

Dextromethorphan hydrobromide is a synthetic compound that belongs to the category of antitussive agents or cough suppressants. It has a melting point ranging from $111^\circ\text{C} - 124^\circ\text{C}$ and a molecular weight of 271.4 g mol\textsuperscript{-1}. It is sparingly soluble in water, freely soluble in ethanol and insoluble in ether, due to which it was included in the BCS-II drug with low aqueous solubility and high permeability (log P = 3.75 and pk\textsubscript{a} = 9.85) and also required multiple dosing due to short biological half-life of 1.4-3.9 h\textsuperscript{3,4}. The mode of action of dextromethorphan is to suppress the cough reflex by a direct action on the cough centre in the medulla of the brain\textsuperscript{4}. The key problem related to this modal drug is not being absorbed efficiently when passed by the intestinal membrane, which leads to poor bioavailability and results in inadequate therapeutic action just because of poor solubility\textsuperscript{1,3,5}. Some additional elements include first-pass metabolism through intestinal cells or liver enzymes (e.g., glucuronidation or oxidation by cytochrome P-450 enzymes, sulfation, etc.) can also restrict its bioavailability (oral bioavailability is 11 %). Various techniques are used to enhance the dissolution rate by improving the solubilization of drugs in the gastrointestinal tract, but intraluminal drug concentration is not mainly limited by the drug solubility in gastrointestinal fluid\textsuperscript{6,7}. Zainab E.J. et al. found that drug solubility is enhanced by using the solvent evaporation method to formulate a cocrystal but the limitation of this study is that the prolonged effect of the drug is not described\textsuperscript{8}. Sai Sathavahana C. et al. reported that the hollow microspheres prepared for controlled release from the optimized formulation at the end of 12 h released only about 79 %\textsuperscript{4}. To attain the drug in free fraction form throughout the process in solution at above-saturated solubility of the drug, which leads to the state of superfluity (supersaturation) and superfluity condition upon transfer to the intestine, as well as to maintain or stabilize polymeric precipitation inhibitors are employed\textsuperscript{9}.

Based on the polymer (hydrophobicity) and drug (hydrogen bond donor and acceptor) properties, polymers with higher molecular weight show better precipitation inhibition\textsuperscript{10}. The natural and semi-synthetic polymeric precipitation inhibitors have been used widely in the enhancement of dissolution rate as well as bioavailability of oral controlled drug delivery system\textsuperscript{11}. These polymers

\textsuperscript{a} Department of Pharmacy, Guru Gobind Singh College of Pharmacy, Yamuna Nagar-135 001, Haryana, India
\textsuperscript{b} Department of Pharmaceutics, MM College of Pharmacy, Maharishi Markandeshwar (DU), Mullana-133 207, Ambala, Haryana, India
\textsuperscript{*}For Correspondence: E-mail: anujmalik007@gmail.com

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act as controlled and prolonged-release agents with mucoadhesive properties. The main influence of drug-release retarding polymer is to maintain the superfluity drug delivery system.

The main purpose of this preliminary research work was to investigate the influence of natural and semi-synthetic polymers on superfluity (supersaturation) potential in gastrointestinal fluid from the non-formulated drug. The solution stability and relationship between equilibrium solubility and degree of supersaturation were also investigated.

MATERIALS AND METHODS

Dextromethorphan hydrobromide was a gift sample from JRC Pvt. Ltd., Gujarat. The procurement of all polymers has been done from Qualikems Fine Chem. Pvt. Ltd. (Vadodara, India), N-N-dimethyl Formamide (DMF) was purchased by Nice Chemical (P) Ltd. (Kerala, India) and the reagents used in this research work were of analytical grade. The superfluity assay was estimated by using SHIMADZU UV-1800 240V (Model) PC dual beam UV spectrophotometer-version 2.4 (Japan).

Solution stability

Solution stability was analyzed over 72 h at room temperature. The preparation of sample solutions was done in the simulated gastric fluid sans pancreatin (SGFsp, 1.2 pH), simulated intestinal fluid sans pancreatin (SIFsp, 6.8 pH), and phosphate buffer solution (PBS 7.4 pH) for the dissolution test. Aliquots (1 mL) were collected initially and at 24 h intervals for 3 days and analyzed spectrophotometrically. The drug concentrations observed in samples at 0, 24, 48, and 72 h were compared. The absolute differences between the results at time zero and the time of analysis indicate the extent of stability.

Induction of superfluity (super-saturation)

The induction and evaluation of superfluity potential can be done before the development of superfluity formulation i.e.; for non-formulated drugs. The initial step for evaluation is to estimate the ability of precipitation inhibitors as well as superfluity behavior in selected medium.

Determination of equilibrium solubility

The equilibrium solubility of dextromethorphan HBr was determined by the conventional shake flask method with and without natural and semi-synthetic polymers (17-19) (xanthan gum, carboxy methyl cellulose sodium (sodium CMC), hydroxypropyl methylcellulose (HPMC 15cps) and mixture of both (HPMC 15cps + xanthan gum) with 1:1 ratio) at a concentration of 0.1 % w/V. Before adding an excess amount of crystalline compound to the test medium, i.e., simulated intestinal fluid sans pancreatin (SIFsp) (pH 6.8) prepared according to the United States Pharmacopeia (USP) protocol and phosphate buffer solution (PBS) (pH 7.4), the polymer was pre-dissolved in the medium under the non-sink condition at a concentration of 1 mg mL⁻¹. The drug–polymer solution was equilibrated at 37 °C for 24 h. Dextromethorphan HBr was detected by ultraviolet (UV) absorbance detection at a wavelength of 278 nm.

Determination of superfluity potential

The superfluity of the drug in SIFsp with and without polymers (0.1 % w/V) HPMC 15cps, sodium CMC, xanthan gum, and a mixture of both (HPMC 15cps + xanthan gum) with 1:1 ratio) was induced using a solvent shift method. The concentration of the drug in the stock solution was found by determining the maximum concentration in the acceptor media before precipitation at a total dimethyl formamide (DMF) concentration of 2 % V/V as organic phase. Standard curves for the given drug were prepared by adding aliquots of the drug dissolved in DMF into SIFsp and PBS until immediate precipitation was recorded by a decrease in absorbance at time intervals. All experiments were conducted at 37 °C under non-sink conditions.

The stock solution was used to induce superfluity in SIFsp and PBS, 0.2 mL of stock solution was spiked into 20 mL SIFsp and PBS.
respectively, and stirred with a magnetic bead on magnetic stirrer (with a hot plate) at 100 ± 3 rpm as shown in Fig. 1.

After adding the DMF stock solution to the test medium, samples (1 mL) were taken at 10 minute intervals up to 3 h. Samples were filtered by using a 0.2 µm filter medium and analyzed by UV spectrophotometer. Three replicates of each superfluity experiment were carried out for each test medium. The data is presented as mean ± SD.

Data investigation and interpretation

The superfluity data were presented as the degree of superfluity (supersaturation) can be determined by using equation (1). For example, the degree of superfluity equal to 30 means that 30 times the amount of drug was dissolved compared to the equilibrium solubility in the corresponding medium with and without polymers.

\[ SSP = \frac{C_t}{C_{eq}} \] (1)

where \( C_t \) and \( C_{eq} \) represent the concentration of the drug at time interval “t” i.e.; 3-4 h (superfluity state), and solubility of the drug at equilibrium i.e.; 24 h (saturation). SSP represents supersaturation potential.

- SSP < 1: subsaturated
- SSP = 1: saturated
- SSP > 1: supersaturated

RESULTS AND DISCUSSION

Stability determination

The two major parameters while choosing the dissolution medium, i.e., solubility of pure drug with and without polymers and solution stability, must be considered. If standard solutions are not stable in a dissolution medium for at least 24 h at ambient temperature, they should not be chosen. Stability study results (Table I) revealed that the change in concentration of drug samples stored in different dissolution media (SIF\textsubscript{sp}) at room temperature over 3 days was less than 10% of that of reference solutions. This indicates that the simulated intestinal fluid (pH 6.8) shows better solution stability as compared to others, but in PBS (pH 7.4) the percentage difference is stable after comparing with 24 h, 48 h, and 72 h, which reveals that for dissolution studies both medium SIF\textsubscript{sp} and PBS are the stable media and so used for future studies depending upon the formulation type.

Effect of polymer on equilibrium solubility of dextromethorphan HBr

The equilibrium solubility of crystalline dextromethorphan HBr is 7.9924 µg mL\(^{-1}\), and the apparent solubility of dextromethorphan HBr increases in the presence of polymer, but the higher equilibrium solubility is found in the combination 1:1 ratio (xanthan gum + HPMC 15cps) as compared to other polymers in both the media, as shown in Fig. 2 and Table II.

Table I: Solution stability profile of dextromethorphan HBr (n=3)

<table>
<thead>
<tr>
<th>Dissolution medium</th>
<th>pH 6.8 (SIF\textsubscript{sp})</th>
<th>pH 7.4 (PBS)</th>
</tr>
</thead>
<tbody>
<tr>
<td>24 h</td>
<td>48 h</td>
<td>72 h</td>
</tr>
<tr>
<td>0-h Conc. (µg mL(^{-1}))</td>
<td>Conc. (µg mL(^{-1}))</td>
<td>% Difference with 0-h</td>
</tr>
<tr>
<td>SGF\textsubscript{sp}</td>
<td>1.2</td>
<td>11.642±0.0033</td>
</tr>
<tr>
<td>SIF\textsubscript{sp}</td>
<td>6.8</td>
<td>10.275±0.0036</td>
</tr>
<tr>
<td>PBS</td>
<td>7.4</td>
<td>10.258±0.0033</td>
</tr>
</tbody>
</table>

Table II: Impact of polymers on solubility for 24 h (SD ± n=3)

<table>
<thead>
<tr>
<th>Polymer (0.1 % w/V)</th>
<th>Solubility (µg mL(^{-1})) 24 h</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>pH 6.8 (SIF\textsubscript{sp})</td>
</tr>
<tr>
<td>Without polymer</td>
<td>7.9924±0.10</td>
</tr>
<tr>
<td>HPMC (15cps)</td>
<td>9.2377±0.0014</td>
</tr>
<tr>
<td>Xanthan gum</td>
<td>14.8981±0.0003</td>
</tr>
<tr>
<td>Na CMC</td>
<td>9.3792±0.0009</td>
</tr>
<tr>
<td>1:1 ratio (HPMC+XG)</td>
<td>19.944±0.0120</td>
</tr>
</tbody>
</table>
Maintenance of superfluity (supersaturated) action by polymers

As shown in Fig. 3, dextromethorphan HBr precipitated rapidly and the concentration decreased, indicating that almost no supersaturation was formed. Maintaining the superfluity state with a polymer matrix is evaluated by SSP. Sodium CMC can enhance dextromethorphan HBr solubility, but it has little role in maintaining supersaturation for a prolonged time. It can be seen from Fig. 3 that HPMC (15cps) and xanthan gum can inhibit the crystallization of dextromethorphan HBr from the supersaturated solutions and significantly prolong supersaturation time, acting as “parachutes” and “gliders”. According to solubility studies, HPMC (15cps) has little effect on dextromethorphan HBr solubility, so the crystallization inhibition role of HPMC (15cps) is based on kinetics. HPMC (15cps) and xanthan gum have a better inhibition role than sodium CMC. The presence of pre-dissolved HPMC (0.1 % w/V) provided a pronounced and stable supersaturation (~134.64 µg mL⁻¹, ~171.58 µg mL⁻¹) in SIF₉ (6.8 pH) and PBS (7.4 pH), respectively. The presence of pre-dissolved xanthan gum (0.1 % w/V) led to a comparable supersaturation (~98.6 µg mL⁻¹, ~126.85 µg mL⁻¹) in SIF₉ (6.8 pH) and PBS (7.4 pH), respectively. It was considered that from Fig. 3, the stability of the superfluity state is not maintained during the time of period of the mixture of pre-dissolved polymers in the media. So, the sodium CMC polymer was not used for future studies.

As shown in Fig. 4, dextromethorphan HBr precipitated after a few minutes and the concentration decreased, indicating that almost no supersaturation was formed. It was observed in Fig. 4 that HPMC and xanthan gum can inhibit the crystallization of dextromethorphan HBr from the supersaturated solutions and significantly prolong supersaturation time, acting as “parachutes” and “gliders”. The superfluity potential of dextromethorphan HBr was improved in the presence of polymers, and the degree of enhancement was dependent on the polymer species in a different medium. In SIF₉, the degree of superfluity (supersaturation) peaked at around 15.53±0.0117, 13.06±0.0116, 6.804±0.0111 and 6.3347±0.005 in the presence of HPMC, CMC sodium, xanthan gum and 1:1 ratio (HPMC + xanthan gum), respectively. Whereas the impact of 1:1 ratio (HPMC + xanthan gum) was relatively small. In contrast, HPMC, CMC sodium,

<table>
<thead>
<tr>
<th>Polymer (0.1 % w/V)</th>
<th>Average SSP</th>
<th>Polymer gain factor</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>SIF (pH 6.8)</td>
<td>PBS (pH 7.4)</td>
</tr>
<tr>
<td>Without polymer</td>
<td>1.0791±0.00078</td>
<td>1.368547±0.005</td>
</tr>
<tr>
<td>HPMC</td>
<td>23.954±0.0136</td>
<td>9.247234±0.004</td>
</tr>
<tr>
<td>Xanthan gum (XG)</td>
<td>11.012±0.0111</td>
<td>8.26817±0.004</td>
</tr>
<tr>
<td>HPMC+XG (1:1)</td>
<td>8.1637±0.033</td>
<td>7.392325±0.0001</td>
</tr>
</tbody>
</table>
and xanthan gum dramatically increased the degree of superfluity (supersaturation) of dextromethorphan HBr up to approximately 15, 13, and 7, respectively. The impact of CMC sodium on dextromethorphan HBr superfluity (supersaturation) was especially large, and the appearance of the superfluity (supersaturation) peak was delayed to a later stage of the dissolution test (180–200 min). Therefore, the utilization of CMC sodium was ignored in further research. Although the effect of each polymer on supersaturation was maintained for a long period dependent upon the polymer species, the apparent rank order of the polymers for maintaining supersaturation potential for at least 3-4 h (HPMC > xanthan gum > CMC sodium > 1:1 ratio (HPMC + xanthan gum)) was identical for dextromethorphan HBr as shown in Fig. 3.

Inhibition of precipitation by polymers mediation on superfluity potential

As significant precipitation was observed, two pharmaceutical polymers, HPMC, and xanthan gum, and their mixture (1:1 ratio) were selected to test their precipitation inhibitory capacity in SIF_{sp} (6.8 pH) and PBS (7.4 pH). The selection of polymers was motivated by their presence as precipitation inhibitors from superfluity (supersaturation) studies. As a clear judgment on the precipitation inhibitory capacity of excipients requires assessment of possible solubilizing effects, thermodynamic and kinetic solubilities were determined in SIF_{sp} (6.8 pH) and PBS (7.4 pH) including 0.1 % w/V polymers. At the applied concentration, HPMC and xanthan gum had a significant influence on the superfluity potential, inducing an up to 22.19 and 10.20-fold, respectively, increase in superfluity potential as compared to a mixture of both polymers (Table III). The order of polymer gain factor on superfluity potential as compared to a mixture of both polymers including HPMC and xanthan gum SD ± (n = 3)

CONCLUSION

This work elucidates the superfluity potential of different polymers used to inhibit precipitation (HPMC 15cps, xanthan gum, and sodium CMC) were taken as polymeric precipitation inhibitors to maintain the superfluity condition of dextromethorphan HBr (non-formulated state). Out of all polymers used in this study, HPMC and xanthan gum, both at 0.1 % w/V, showed excellent precipitation inhibitor effect by maintaining the superfluity potential at about 10.2-22.1 factor in SIF_{sp} and 6.04-6.75 factor in PBS (pH 7.4). Consequently, the above result indicates that HPMC (15cps) is based on the concept of parachute and xanthan gum on the glider concept and shows the novelty of this work. Hence, the knowledge derived from this preliminary study is that the main influence of these polymers is to maintain the superfluity potential. For the selection of suitable polymers before preparing any formulation or for non-formulated drug conditions used to develop the superfluity formulation with the rationalized polymers, a solvent-shift method was used for the determination of superfluity potential. For more clarification of polymers selection and their action for prolonged action with bioavailability improvement relating to pH variation in GIT, pH-Shift method was carried out to evaluate the superfluity behavior.

FUTURE PERSPECTIVES

The future work includes the investigation of superfluity potential by using other natural and synthetic polymers which are not discussed earlier with the model drug. The analysis of superstation conditions can be done by using the pH-shift method for a more comparative study. In this preliminary research work, only the investigation of the model drug is done in the form of a non-formulated drug. The superfluity formulation can be developed by using different techniques such as amorphous solid dispersion, supersaturate-self-micro emulsifying drug delivery system, supersaturate-liposomes, etc., which can lead to the improvement in bioavailability of the drug along with prolonged release effect. As a result, this multiple dosing problems are also resolved and from this secondary problem, drug abuse and toxicity are also reduced.

REFERENCES


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