DESIGN AND DEVELOPMENT OF MOUTH DISSOLVING FILM OF KETOROLAC BY USING NOVEL POLYMERS

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ABSTRACT

Introduction: Ketorolac is a non-steroidal anti-inflammatory drug. It is used to treat severe pain and also used post-operative pain surgery. Ketorolac is class first according BCS class therefore it shows maximum bioavailability and permeability.

Material and Method: Ketorolac mouth dissolving film were prepared by using solvent casting method. Thereafter evaluation parameter to be evaluated like Weight, Thickness, Drug content, Dissolution study, Franz Diffusion, FTIR, DSC, tensile Strength.

Result and Discussion: Mouth dissolving film were prepared by using solvent casting method. Two polymer were used for the preparation film and evaluated so it was observed that Batch 4 shows maximum drug content 98.60% and shows 95.11% drug release in 5 min.

Conclusion: Ketorolac Mouth Dissolving Film prepared and evaluated so it was found that batch 4 shows maximum drug release as compare to other batches.

Keyword: Mouth Dissolving Film, HPMC E15, HPMC E5 and Anti Inflammation.

I. INTRODUCTION

At present situation formulation research modified in such way that, drug targeting to different site via various targeting drug delivery system. Instead of developing generic molecule formulator prefer new drug delivery system and avoiding tedious molecule development process. Oral drug delivery is mostly preferred drug delivery and commonly used drug delivery system there are certain advantages like dose uniformity, self-use and stable delivery. (1) Oral thin film was first develop in 1970 as a novel dosage form and film were launched in 2004 for systemic drug delivery. (2) Fast dissolving oral disintegrating film in advance form which instant drug release from dosage form (within 1 min) and rapid absorb via mouth as a result quick reach into blood circulation hence maximum bioavailability is been achieved.

There are criteria to incorporate API into film like drug should have low molecular weight, less dose, should not be bitter, it should be absorb via mouth. Then only we can formulate oral thin film. Most commonly thin film having the area 2x2 cm², due to more surface area is help to dissolve or disintegrate easily and within less time it reach into systemic circulation. (3) Oral thin film contain some water soluble polymer, saliva stimulating agent, sweetener and plasticizer. Some hydrophilic polymer form matrix so within that matrix incorporate drug when it come in contact with saliva it will quickly disintegrate and absorb fastly. (2) Polymer plays an important role while making film some synthetic polymer like HPMC, HPMCE-15, HPMCE-5, PVA and Natural like Pullulan is used. Sweetener is used to mask bitter taste ex. Sodium Saccharin, Sucralose. Plasticizers is used to maintain flexibility and elastic nature of film Ex. PEG-400, Tween-80.

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Ketorolac is non-steroidal anti-inflammatory drug. Which is used to treat severe pain and also used post-operative pain surgery. Ketorolac is class first according BCS class therefore it shows maximum bioavailability and permeability. KT administration rate is frequent as it has short plasma half-life 3-6 h. The frequent intake of NSAIDS like KT leads to gastric ulceration, bleeding and other gastric complications. Due to problem like gastric ulceration and bleeding we had selected mouth dissolving film. It avoid first pass metabolism and it directly reach into blood circulation.(4)

The disease like allergy, hypertension, angina, epilepsy, severe pain dominantly treat by using film mostly commonly used in pediatrics, Geriatrics, Bedridden patient. Those drug shows first pass metabolism, gastric irritation, having less dose and less molecular weight it will be eligible for making film formulation.(3)(4) Generally 45% w/w of polymer used based on total weight of film concentration of polymer decide transparency of film. High amount of polymer leads to thickness of film as a result more time take for disintegration it means more time required for dissolution and bioavailability.

II. MATERIAL AND METHOD

Material
Ketorolac was obtained as gift sample from Sun Pharmaceutical Vadodara Gujrat. Hydroxy Propyl Methyl Cellulose E5 & E15 (Yarrow chem product Mumbai), Polyethylene Glycol & Tween 80 (Modern Industry Sinner), Sodium Benzoate (LobachemPvt.Ltd.Mumbai), Sodium Saccharin (Research Lab Fine Chem Mumbai).

Method
Formulation of Film
Formulation of mouth dissolving film prepared by using solvent casting method. Initially weight all excipient accurately, take few quantity of water to it add HPMC E15 and HPMC E5 in two separate beaker. Stir both polymeric solution by using glass rod until it become clear solution. After that mix both polymer solution and keep it 30 min for sonication. In another beaker dissolve sodium benzoate and sodium saccharin into water, stir this until completely solution then add this solution into above polymeric solution. Thereafter addition of PEG-400 dropwise into the above solvent along with tween-80. At the finally dissolve drug into separate beaker into the water and pour this solution into above mixture. Sonicate the solution for 30 min for removing air bubble from mixture. Then add solution into Petri dish and kept into oven for 24 hr at 40 °C. After drying of film cut into 2*2 cm pieces.

Dose Calculation
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Dose of Ketorolac is 10 mg, therefore the dose required in the 2*2 cm² film is 10 mg

Area of Circle = \( \pi r^2 \)

Hence Radius is 3.75 cm

Therefore Area = \( 3.14 \times (3.75)^2 \) = 44.15 cm²

Therefore dose for 44.15 cm² is 110.3 mg

**Composition of Film**

Mouth Dissolving Film composition consist of Drug, water soluble polymer, plasticizer, Preservative and sweetener. Different concentration of HPMC E15 & HPMC E5 used for this formulation. By using NCSS factorial design software we had prepared batches 3² factorial Design.

<table>
<thead>
<tr>
<th>Table No 01: Composition of Film</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Ingredient</strong></td>
</tr>
<tr>
<td>Drug (mg)</td>
</tr>
<tr>
<td>HPMC E15 (mg)</td>
</tr>
<tr>
<td>HPMC E5 (mg)</td>
</tr>
<tr>
<td>Citric Acid (mg)</td>
</tr>
<tr>
<td>PEG-400 (ml)</td>
</tr>
<tr>
<td>Tween 80 (ml)</td>
</tr>
<tr>
<td>Sodium Saccharin (mg)</td>
</tr>
<tr>
<td>Sodium Benzoate (mg)</td>
</tr>
<tr>
<td>Pineapple Flavour (mg)</td>
</tr>
<tr>
<td>Water (ml)</td>
</tr>
</tbody>
</table>

**Preformulation Study**

1 **DSC**

The DSC thermogram of ketorolac is characterized by sharp endothermic peak at 170°C which corresponding to melting point of ketorolac. The DSC scan of physical mixture also showed a sharp melting at 170°C. It is clear that there is no change in the position of the characteristic peak of the drug in the physical mixture. (DSC graph given in Fig No 06 & 07)
2 FTIR

FTIR study used to determine chemical structure of drug molecule as well as to check compatibility of formulation. If any functional group shows interaction with drug molecule then changes in peak. So in this formulation all peak of drug molecule same as it is in complex formulation so it indicate that no interaction between drug molecule and excipient. (FTIR Spectra given in 08,09,10&11)

3 Melting Point Determination

Melting point determination is qualitative test for determination of drug molecule. Thiel tube method were used to determine melting of ketorolac and it was found that 167 °C.

So it was confirm that given drug sample is ketorolac.

Evaluation

1 Appearance, Size, Shape and Thickness

Thickness of film decide the dissolution rate, if the film thick then dissolution rate will be less and vice versa. Thickness of determine 5 different location of film and then calculate the mean.(5) Thickness of film check by using Digital Vernier Caliper(6), Micrometer Screw Guage and Dial Guage Tester(7).

2 Weight Variation

Weight variation plays an important role to maintain dose uniformity of each film. Cut film 2*2 cm² and check weight of film by using Digital analytical Balance. Weight of three film measure and take mean. This test also useful to ensure that film contain proper amount of drug and Excipient. (6)(5). Weight variation of formulation given in table no 03.

3 Folding Endurance

Initially film were cut, then film fold into repeated time at same point until break. The number of time film folding until break is called Folding Endurance Value. Typical value for folding endurance is between 100-150.(8)(9). Folding Endurance of the formulation given in 03.

4 Tensile Strength

This test is used to determine mechanical properties of film.(11) Tensile strength basically depends on the concentration of polymer used in the formulation. It can be determine using texture analyser (12) and Digital tensile tester.(13) Tensile strength means maximum stress applied at which film break. It can be calculate by using following formula (14) Tensile Strength Graph of the formulation given in Fig No 13.

\[
\text{Tensile Strength} = \frac{\text{Load at Failure}}{\text{Strip Thickness} \times \text{Strip Width}} \times 100
\]

5 PH Determination

Cut film into 2*2 cm², add film into petri dish containing 5 ml distilled water. After few minute check PH of solution by using digital PH meter. (15) PH of mouth dissolving film given in Table No 03.

6 Drug Content

Drug Content parameter indicate the how much amount of drug present in the formulation. Whatever amount of drug we are going to load into the formulation to check is is load successfully or not, this parameter used. Most commonly drug content determine with the help of UV spectrophotometer. (16) Drug Content of formulation given in table no 03.
7 **In Vitro Drug Release Study**

In vitro drug release study determined with the help of USP type 2 (Paddle Apparatus) how much amount of drug release from formulation with respect to time. This test done by using 900ml Phosphate buffer 6.8 using paddle apparatus. Aliquot withdraw every one minute time to upto 5 min time. Calculate % Drug release with the help of UV Spectroscopy.(17)(18) Dissolution study data given in table no 04 and fig no 04.

\[
% \text{ Drug Release} = \frac{\text{Conc} \times \text{Dil.Factor} \times \text{Disso. medium}}{1000} = \frac{\text{Above Value}}{\text{dose of drug}} \times 100
\]

![Fig No 02: Dissolution Study of Mouth Dissolving Film](image1)

8 **In Vitro Disintegration Time**

Cut film in 2*2 cm², dissolve into 10 ml distilled water and note the time required to disintegrate film. (19)

9 **Franz Diffusion Cell**

Franz Diffusion Cell apparatus used to check permeability of drug inside the membrane. It consist two cell (receptor and donor). On the receptor compartment add Phosphate buffer 6.8 and in the donor compartment keep film formulation. Within two compartment there is presence of semipermeable membrane. With respect to time drug cross the semipermeable membrane and enter into the receptor compartment fluid.(20)Franz Diffusion study data given Fig no 05.

10 **Scanning Electron Microscopy**

The SEM photographs of MDFs showed smooth surfaces without any scratches so it indicating that Ketorolac is uniformly distributed. Some crystal images shows in the photograph but it does not effect on the Dissolution study.(21) SEM images of formulation given in fig no 12.

11 **Stability Study**

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Stability study carried out in stability chamber with maintaining temperature and relative humidity at 40˚C and 75% RH Respectively. Sample was packed in butter paper and aluminium foil and subjected for study. Sample study carried out in 0, 30 and 90 day. Appearance of film, disintegration time and % drug release checked of optimised batch.(12) Stability Study data given table no 02.

Table No 02: Stability Study Data

<table>
<thead>
<tr>
<th>Sr.No</th>
<th>Time ( Days )</th>
<th>Appearance</th>
<th>Disintegration Time</th>
<th>% Drug Release</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>0</td>
<td>Transparent</td>
<td>54</td>
<td>95.11</td>
</tr>
<tr>
<td>2</td>
<td>30</td>
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<td>94.97</td>
</tr>
<tr>
<td>3</td>
<td>90</td>
<td>Transparent</td>
<td>56</td>
<td>94.16</td>
</tr>
</tbody>
</table>

Fig No 03: Stability Study of Mouth Dissolving Film

III. CONCLUSION
Mouth Dissolving Film of ketorolac was prepared by using solvent casting method. HPMC E15 and HPMC E5, PEG400 & Tween 80 were involve in this formulation. By changing the concentration of two polymer film were prepared and evaluated. So it was found batch four gives outstanding result of all evaluation. Film disintegrate in 54 second and shows 95.11% drug release in 5 min.

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IV. RESULT AND DISCUSSION
Table No 03: Results of Parameter

<table>
<thead>
<tr>
<th>Batch</th>
<th>Weight ( mg )</th>
<th>Surface PH</th>
<th>Disintegration Time ( Sec )</th>
<th>Folding Endurance</th>
<th>Thickness ( mm )</th>
<th>% Drug Content at 5th min</th>
<th>% CDR</th>
</tr>
</thead>
</table>

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<table>
<thead>
<tr>
<th>Batch</th>
<th>1 Min</th>
<th>2 Min</th>
<th>3 Min</th>
<th>4 Min</th>
<th>5 Min</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>26.38</td>
<td>50.84</td>
<td>71.04</td>
<td>90.85</td>
<td>96.44</td>
</tr>
<tr>
<td>2</td>
<td>24.65</td>
<td>46.45</td>
<td>66.67</td>
<td>76.76</td>
<td>93.78</td>
</tr>
<tr>
<td>3</td>
<td>22.52</td>
<td>37.94</td>
<td>64.26</td>
<td>73.57</td>
<td>91.78</td>
</tr>
<tr>
<td>4</td>
<td>21.72</td>
<td>30.63</td>
<td>55.49</td>
<td>74.63</td>
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</tr>
<tr>
<td>5</td>
<td>14.81</td>
<td>31.16</td>
<td>64.00</td>
<td>74.23</td>
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<tr>
<td>6</td>
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<td>50.70</td>
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<td>7</td>
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<td>13.35</td>
<td>26.64</td>
<td>51.10</td>
<td>65.99</td>
<td>85.67</td>
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</tbody>
</table>

Table No 04: In Vitro Drug Release Study

Fig No 04: % Drug Release Graph of all batches
Fig No 05: Franz Diffusion Study of Optimised Batch

Fig No 06: DSC of Ketorolac

Fig No 07: DSC of Ketorolac and Polymer Mixture

FTIR Study
Fig No 08: FTIR of Ketorolac

Fig No 09: FTIR of Ketorolac + HPMC E5
Fig No 10: FTIR of Ketorolac+ HPMC E15

Fig No 11: FTIR of Ketorolac + HPMC E5 + HPMC E15

SEM Images
REFERENCE


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