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FORMULATION AND EVALUATION OF FAST-DISSOLVING ORAL DISINTEGRATED FILM OF VALDECOXIB

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ABSTRACT:
A non-steroidal anti-inflammatory medicine called valdecoxib is used to treat osteoarthritis, rheumatoid arthritis, painful menstruation, and other menstrual-related symptoms. It inhibits cyclooxygenase-2 (COX-2) specifically. In the current investigation, oral Valdecoxib thin films were prepared to have a quicker onset of effect. Oral thin films were prepared by employing the solvent-casting method. Propylene glycol was selected as a permeation enhancer and plasticizer. Drug excipient compatibility studies were carried out by using FT-IR, and it was observed that there were no interactions. Among all the six formulations, DCXB6 is the best formulation with 97.23% drug release. The linearity was found in the concentration range of 1µg/ml to 6µg/ml. The Correlation coefficient was 0.997. The regression equation was found to be Y = 0.127x+0.013. The proposed method was successfully carried out for the formulation and evaluation of fast dissolving oral disintegrated film of valdecoxib**.**

Keywords: Valdecoxib, First dissolving film, Propylene glycol, FT-IR, UV- spectroscopy.

INTRODUCTION:

The oral route is the most preferred route of administration for the systemic effect. Approximately, 60% of all the formulations are solid dosage forms. The tablet is the most preferred dosage form due to ease of transportation, manufacturing and more patient compliance. Generally geriatric, pediatric, bedridden, sudden episodes of allergic attack, coughing, emetics, and emergency (cardiac), patients experience difficulties in swallowing the conventional oral dosage form. To overcome this problem a novel formulation was developed i.e. oral fast-dissolving films or rapidly dissolving films (RDF). Researchers refer to the fast-dissolving dosage forms by a variety of names, including mouth dissolve, quick disintegrating, orally disintegrating, and melt-in-mouth dosage forms[1-3]. However, these dosage forms are

now available on the pharmaceutical markets in the United States and Europe for [4-7] therapeutic benefits. When placed on the tongue in the oral cavity, a film or strip that is made of water-soluble and/or water-swellable film-forming polymer dissolves instantly. The first oral strips of this type were created by the well-known pharmaceutical corporation Pfizer and were known as Listerine® pocket packs™. They were used to freshen the mouth. The first therapeutic oral thin films were Chloraseptic® relief strips which contained [7] benzocaine and were used for the treatment of sore throat. Oral fast-dissolving films are also useful for local effects such as local anaesthetic for toothache, oral ulcers, and cold sores or coughing. It improves the efficacy of active pharmaceutical ingredients (APIs) compared to fast-dissolving tablets, by dissolving in the oral cavity after contact with less saliva without chewing and no need for water for administration. The delivery system consists of a thin film, which is placed on the patient's tongue or mucosal issue, instantly wet by saliva; the film rapidly dissolves. Then, it rapidly disintegrates and dissolves to release the medication for oral mucosal absorption. It improves the efficacy of API within a minute dissolved in the oral cavity after contact with saliva without chewing and no need for water for administration. Fast dissolving action is primarily due to the large surface area of the film, which wets quickly when exposed to the moisture environment. The fast-dissolving drug delivery system is specially designed for drugs which have extensive first-pass metabolism and have low doses, for the enhancement of bioavailability.

The Rapidly dissolving films (RDF) are essentially prepared using water soluble and fast disintegrating polymers which also possess good film-forming properties like Hydroxypropyl methylcellulose (HPMC, E5), Methylcellulose (MC), Polyvinylpyrrolidone (PVP), Polyvinyl alcohol (PVA), and sodium carboxymethylcellulose (SCMC) with super disintegrants like Sodium Starch Glycolate **(**SSG), carboxymethylcellulose sodium (CCS) and polyplasdone XL-10 of Captopril[8]**.** Valdecoxib is a non-steroidal anti-inflammatory drug used in the treatment of osteoarthritis, rheumatoid arthritis, and painful menstruation and menstrual symptoms[9].Chemically valdecoxib is known as 4-(5-methyl-3-phenyl-1, 2-oxazol-4-yl) benzene-1-sulfonamide (Figure 1). Valdecoxib is categorized as a nonsteroidal anti-inflammatory drug (NSAID) and is a selective cyclooxygenase-2 (COX-2) inhibitor. In the treatment of dysmenorrhea or acute pain, as well as for the management of osteoarthritis (OA), valdecoxib is utilized for its anti-inflammatory, analgesic, and antipyretic properties. Unlike celecoxib, which needs CYP450 enzymes for metabolism, valdecoxib doesn't have a sulfonamide chain. Arachidonic acid is transformed into prostaglandin (PG) H2, which is a precursor of PGs and thromboxane, through the action of COX-1 and COX-2. The cyclooxygenase-2 (COX-2) enzyme, which is crucial for the modulation of pain and inflammation, is selectively inhibited by the drug valdecoxib. In terms of safety, valdecoxib is superior to conventional non-steroidal anti-inflammatory drugs since it is well tolerated, has minimal gastrointestinal toxicity, and has no impact on platelet function.

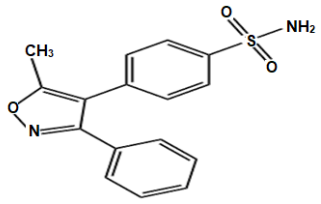

Figure 1: Structure of Valdecoxib

The Valdecoxib films are made to disintegrate quickly in contact with a wet surface, such as the tongue, so the user can take the medication without the addition of liquid. This simplicity might boost patient compliance while also giving marketers a marketing advantage. The first-pass effect and gastrointestinal tract degradation can be avoided because the drug is directly absorbed into the systemic circulation. Due to these factors, this formulation is particularly popular with geriatric and paediatric patients as well as those who are afraid of choking. The fast-dissolving film is a more acceptable and accurate oral dosage form which bypasses the hepatic system and provides a therapeutic effect/response[10]**.** Different methods like Solvent casting, Hot-melt extrusion, Solid dispersion extrusion, Rolling method, and Semisolid casting, respectively were used to prepare the oral films in large volume as well as small volume

production. One or a combination of the above process (s) may be used for the preparation of oral films. There are many techniques available to prepare oral films such as; Taste Masking, Orally Disintegrating films (ODF), Vaccination, and Sustained Release film applied for administration of films for effective therapeutic value. The current study aims to develop and describe fast-acting oral films of valdecoxib for quick drug dissolution and absorption, which may result in a rapid commencement of an action in the treatment of pain. The study also aims to improve the bioavailability of the drug.

MATERIALS AND METHODS:

Valdecoxib bulk drugs were generously provided as a gift sample by Hetero Labs, Hyderabad, India. Sodium alginate (Signet Chemical Corporation, Mumbai, India), Xanthan gum and Citric Acid (SD fine chemicals, Mumbai, India.), PVP K30, Propylene Glycol and Aspartame (Merck Specialities Pvt. Ltd, Mumbai, India) were used in the study.

A brief study has been made on various parameters by using UV-Spectrophotometer (Shimazu- UV1900), FT-IR (Brukur-210329) and Digital pH meter (Auto pH meter-pH700, Eutech), Franz diffusion cell (Borosil-EDC 07A) to evaluate such films.

Fast-dissolving oral disintegrated films of valdecoxib were prepared by using the Solvent casting method. Before the preparation of oral disintegrated films, a standard curve of Valdecoxib in pH 6.8 saline phosphate buffer was obtained to quantify the samples. All solutions were freshly prepared before use. To quantify the samples, we have prepared a standard curve of Valdecoxib for the preparation of oral disintegrated films using saline phosphate buffer (pH 6.8). After creating successive dilutions of the medication from a stock solution (0.1 mg/ml), calibration curves for valdecoxib were drawn using phosphate buffers (pH 6.8). Samples were then examined by spectrophotometric technique for valdecoxib at its λ max (244 nm)[11].

Preparation of saline phosphate buffer

About 1 gm of potassium dihydrogen orthophosphate, 2 gm of dipotassium hydrogen orthophosphate and 8.5 gm sodium chloride were added to water in one litter volumetric flask. The contents are thoroughly mixed to get a clear solution. The volume was made up of 900 ml of water. The pH was adjusted to 6.8 with 0.2-mole phosphoric acid or sodium hydroxide solution [12].

Preparation of standard solution of Valdecoxib

Accurately weighed 100 mg of Valdecoxib was placed in a 100 ml volumetric flask and to this 50 ml of ethanol was added to dissolve the drug. The volume was made up to 100 ml using ethanol to give 1000 mcg/ml solution (stock solution–I). A 10 ml aliquot was taken and placed in a 100 ml volumetric flask and diluted with water to 100 ml to get 100µg/ml (stock solution -II). From stock solution II, 10 ml of aliquot was diluted to 100 ml to obtain10µg/ml (stock solution III). Similar dilutions were performed from stock solution -I in different media like 6.8 pH saline phosphate buffer.

Absorption maxima (λ_{max}) for Valdecoxib

A 10µg/ml standard solution of Valdecoxib was scanned on a double-beam spectrophotometer against respective media blanks. An absorption maximum (λ_{max}) of 225nm was obtained for all solutions and was selected to prepare the standard curve[13].

Preparation of standard curve for Valdecoxib

Standard curves for Valdecoxib were obtained in water, 6.8 pH saline phosphate buffer. Aliquots of 1 ml, 2 ml, 3 ml, 4 ml, 5 ml and 6 ml of Valdecoxib standard solution of 100 µg/ml (stock solution-II) were taken and diluted to obtain concentrations from 10 to 60 µg/ml with appropriate media. The absorbances of solutions were determined at 225 nm against respective media as blank. The experiment was repeated six times for each buffer and a calibration curve was determined from the mean value as shown in figure 2.

Dose calculation

Oral doses of films[14] are generally of stamp size but the range acceptable is around 5-20 cm^2. Each patch with 4 cm^2 was chosen as the optimum size based on dose, ease of handling and administration. The calculation of the total amount of drug required for each petri plate is given below.

Dose of Valdecoxib each film	10 mg
Area of the film designed	4 cm^2
Area of the Petri plate	31.4 cm^2
Amount of polymer solution in each plate	20ml
The amount of drug required for the total plate is around	100mg
Hence per plate, approximately8 films of4 cm^2 were obtained	

Preparation of oral thin films

Oral thin films were prepared by using solvent casting method[15] where Sodium alginate, Xanthan gum, and PVP K30 were weighed in required ratios and they were then dissolved in water (Coldwater) as solvent. Valdecoxib, Propylene glycol was added to the above dispersion under continuous stirring Sweeteners like aspartame were also added to the above solution. Citric acid was also mixed with it. The uniform dispersion was poured into the Petri plate. The rate of evaporation of the solvent was controlled by inverting the cut funnel over the thin films. After 24 hours, the dried thin film was taken out and stored in desiccators as shown in Table 1.

Evaluation of the oral thin film

The evaluation parameters like the thickness of the film, dissolution time, folding endurance, pH, percentage of moisture uptake, and tensile strength are used for the fast-dissolving oral disintegrated film.

Organoleptic evaluation

For evaluation of psychophysical evaluation of the product, special controlled human taste panels are used. In-vitro methods of utilizing taste sensors, specially designed apparatus and drug release by modified pharmacopoeial methods are being used for this purpose. These in-vitro taste assessment apparatuses and methodologies are well suited for high throughput taste screening of oral pharmaceutical formulations.

Thickness measurement

The thickness of the film is measured using a dial gauge tester. Thickness at different points is measured from which the average thickness of the fast-dissolving oral films was determined[16].

Dissolution time

It is defined as the time at which not less than 80% of the tested film is dissolved in aqueous media. It can be done by both *in vitro* and *in vivo* methods. *In vitro,* dissolution time can be determined by keeping the desired piece of film in a Petri dish containing water and noting the time required to dissolve at least 80% of the film. *In vivo* dissolving time of the film is studied by selecting groups of volunteers of different ages. The films of desired size should be kept in their oral cavity till they completely dissolve without any residue left in the mouth and in vivo dissolving time of the film is noted[17,18].

Measurement of folding endurance

To carry out the endurance study, the strip of film is repeatedly folded at the same place until it breaks. The number of times the film is folded at the same place before breaking gives the folding endurance[19].

***In-vitro* dissolution**

The in vitro drug release study of the film was carried out using a USP 23 type 2 rotating paddle dissolution test apparatus. 250ml of phosphate buffer (pH 6.8) was used and maintained at 37 ± 5^0C while the basket was set at 50 rpm. A film sample of 4 cm^2 was fixed onto the specially designed SS disk with the help of cyanoacrylate adhesive. The disk was put at the bottom of the dissolution vessel so that the patch remained on the upper side of the disk. Five millilitres of samples were taken at an interval of 60 sec., and the same amount was replaced with fresh buffer. The withdrawn samples were filtered through Whatman filter paper and then 1ml of the filtered sample was further diluted to 10ml of the same medium and analyzed using a spectrophotometer at a wavelength of 225 nm[20]. The cumulative percentage release

for different formulations was calculated. The relationship between time and percentage release was plotted. The results of *in-vitro* dissolution studies of all formulations.

Moisture uptake

The test is done by keeping previously weighed films in desiccators at a particular temperature and relative humidity. After three days, the film is taken out and reweighed to determine the percentage of moisture uptake. The percentage of moisture uptake can be calculated as follows.

Percentage of moisture uptake = Final weight – Initial weight ×100.

Moisture content

Previously weighed films are stored in a desiccator for 24 hours. The final weight is noted when there is no further change in the weight of individual film[19]. The percentage of moisture content can be calculated as follows,

$$\text{Percentage of moisture content} = \frac{\text{Initial weight} - \text{Final weight}}{\text{Initial weight}} \times 100$$

Tensile strength

Tensile strength is the maximum stress applied to a point at which the strip specimen breaks. The tensile strength of the film is determined by using a tensile testing machine like the Instron or Monsanto tester. It is calculated by the applied load at rupture divided by the cross-sectional area of the strip as given in the equation below.

Tensile strength = Load Failure ×100

Drug excipients interaction studies

FT-IR spectrum interpretation

IR spectral analysis was carried out using FT-IR by the KBr disc method. The sample and KBr were triturated and compressed to get the discs. The samples of pure drug, dummy formulation and optimized formulation were analyzed between wave numbers 4000.0 and 400.0 cm^{-1}.

RESULTS AND DISCUSSION:

Standard Calibration curve of Valdecoxib

Preformulation studies of the model drug i.e. valdecoxib were performed for determining the solubility, melting point and λmax. The results showed that the drug was found to be freely soluble in ethanol, acetone and methanol, sparingly soluble in distilled water and glacial acetic acid while practically insoluble in ether. The melting point of valdecoxib was found to be 163^0C approx. The λmax of valdecoxib was found to be 225nm and the standard calibration curve of valdecoxib was prepared as shown in Figure 2. Fast-dissolving oral disintegrated films of valdecoxib were prepared by solvent casting method as per the formulae given in Table 1.

Table 1: Formulations of Valdecoxib oral thin film

Sl.No	Ingredients	DCXB1	DCXB2	DCXB3	DCXB4	DCXB5	DCXB6
1	Drug (mg)	100	100	100	100	100	100
2	Sodium alginate(mg)	50	100	-	-	-	-
3	Xanthan gum(mg)	-	-	50	100	-	-
4	PVP K30(mg)	-	-	-	-	50	100
4	Propylene glycol(ml)	2	2	2	2	2	2
5	Citric Acid(mg)	5	5	5	5	5	5
6	Aspartame(mg)	3	3	3	3	3	3
7	Water(ml)	20ml	20ml	20ml	20ml	20ml	20ml

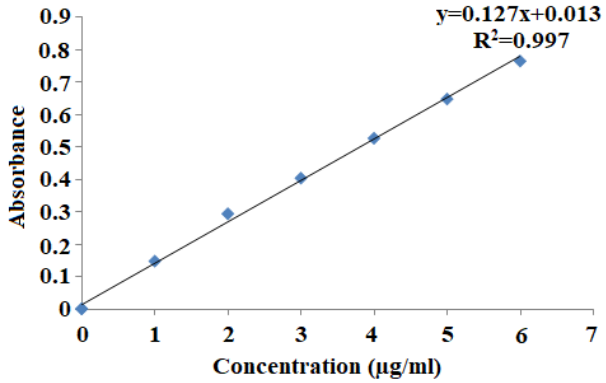

Figure 2: Standard graph of Valdecoxib in pH 6.8 Phosphate buffer (mean±SD; n=3)

FT –IR Compatibility Study

In the current research, an effort has been made to prepare a valdecoxib oral disintegrating film that dissolves quickly using the solvent casting process. FT-IR spectroscopy was employed to investigate any potential interactions between the drug and excipients used in the formulation development of valdecoxib.

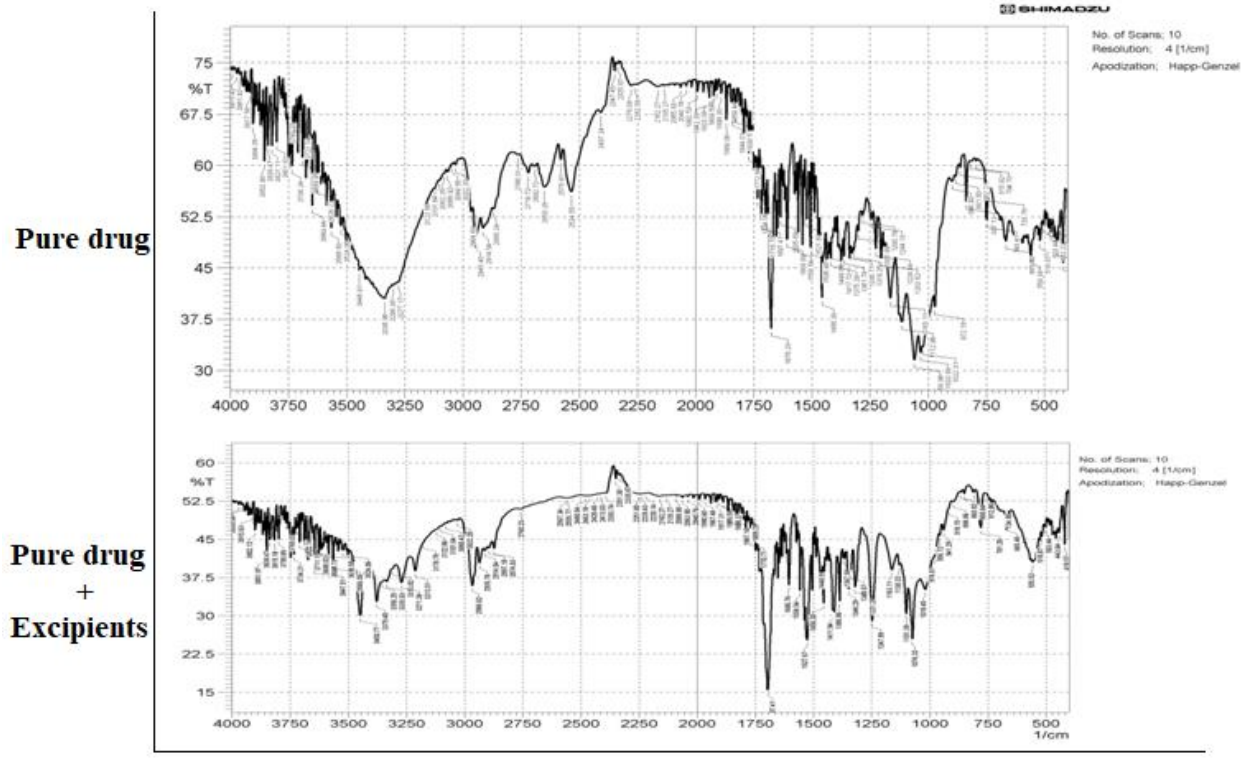

Figure 3: FT-IR spectrum of pure drug and optimized formulation

Figure 3 displays the FT-IR spectra of the drug alone and the drug combined with excipients. The FT-IR spectra of the pure drug valdecoxib showed a distinctive broad absorption band at 3277.17 cm^{-1}, which indicated the presence of the N-H group (NH stretching). An aromatic ring C-H stretching and aliphatic C-H stretching (-CH_3) bands appeared at 3066.66 cm^{-1},2945.40 cm^{-1} and 2868.24 cm^{-1} respectively. Whereas S-O of SO_2 (S=O stretching) causes a distinctive absorption band at 1325.29 cm^{-1} and 1112.98 cm^{-1} to exist. Similarly, the IR spectrum of valdecoxib and other polymers, such as PVP K30, demonstrated characteristic absorption bands for the functional groups N-H, Aromatic CH=CH, aliphatic C-H (-CH_3), and S=O at or near the values of valdecoxib absorption bands, indicating that there was no chemical or physical change in the functional groups present in valdecoxib.

Evaluation of Valdecoxib oral thin films

Based on quality control measures, such as thickness, folding endurance, drug content, moisture uptake, moisture content, weight change, and disintegration duration, the rapid dissolving oral disintegrating film of valdecoxib was evaluated post-compression. Table 2 contains a summary of all the post-compression evaluation outcomes. The thickness of all the formulations was found to range between 0.3482 and 0.3537 mm. All of the formulas performed admirably. Values for folding endurance ranged from 247 to 257. Oral thin films were found to be within the pharmacopoeial limit since the weight variation of the disintegrated oral film from the average was kept to less than 0.1%. The oral disintegrating film's moisture content (%) was found to be between 2.91 to 3.13%, which is within the pharmacopoeial limit. All films' content homogeneity fell between 97.72 and 99.12%, suggesting good uniformity across various film formulations. All formulations' moisture uptake, which was found to range from 2.97 to 3.13%, may have contributed to the formulations' hygroscopic qualities. All of the formulations, DCXB1 through DCXB6, displayed reasonably good disintegration times between 43±0.16 and 48±0.54 seconds (Figure 4).

Table 2: Evaluation of Oral thin films by physical methods

Formulation	Thickness (mm)	Folding endurance	Drug content (%)	Moisture uptake (%)	Moisture content (%)	Weight variation
DCXB1	0.3482	247±0.47	98.06±0.41	3.13±0.13	3.08±0.12	168.13±0.12
DCXB2	0.3463	252±0.54	99.12±0.32	2.89±0.30	3.12±0.33	225.24±0.11
DCXB3	0.3524	247±0.34	98.43±0.42	3.06±0.16	2.97±0.35	172.19±0.65
DCXB4	0.3511	249±0.21	97.72±0.54	2.97±0.65	2.88±0.28	221.06±0.46
DCXB5	0.3499	253±0.11	99.67±0.43	2.86±0.44	2.91±0.17	173.12±0.72
DCXB6	0.3537	257±0.33	98.05±0.24	3.03±0.23	3.05±0.19	220.17±0.21

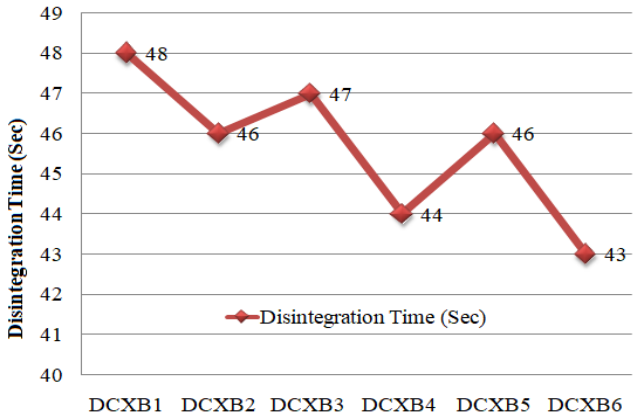

Figure 4: Disintegration time for oral thin films of (DCXB 1- DCXB 6)

Physical appearance (colour, clarity, and flexibility), thickness, and weight variation disintegration time, among other examination techniques, all indicated that the results were within pharmacopoeia limitations. All of the fast-dissolving oral disintegrating films for valdecoxib were discovered to be flat and free of foams when flatness was taken into consideration. Using USP apparatus II, the *in-vitro* drug release from the film of each formulation was carried out in triplicate (paddle method). A dissolution investigation was conducted in phosphate buffer at pH 6.8. For the formulations of DCXB4 and DCXB6, approximately 90.14% and 97.23% of the medication were released in 30 minutes (Table 3). Around 88.61% and 88.32% of the drug in the DCXB2, DCXB5 formulation was released in 30 minutes. According to this drug release pattern, drug release is increased when plasticizer concentration is higher and decreased when polymer concentration is higher (Figure 5).

Table 3: Cumulative % Drug release of formulation DCXB1 to DCXB6

Time (Min)	DCXB1	DCXB2	DCXB3	DCXB4	DCXB5	DCXB6
5	19.07%	23.52%	21.06%	27.04%	24.37%	22.07%
10	35.53%	39.31%	38.73%	38.29%	40.12%	39.85%
15	47.14%	54.19%	53.18%	46.05%	51.73%	58.76%
20	58.91%	64.81%	69.07%	58.71%	65.91%	70.83%
25	77.54%	75.04%	76.85%	69.35%	78.64%	86.11%
30	84.05%	88.61%	83.77%	90.14%	88.32%	97.23%

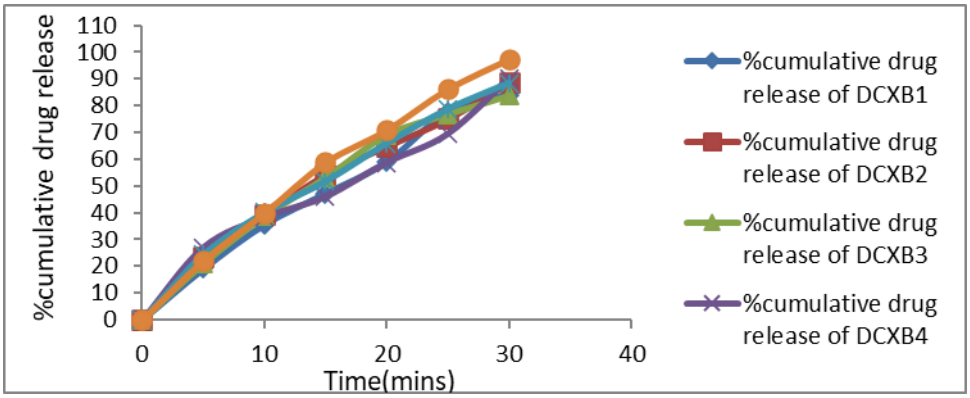

Figure 5: *In-vitro* dissolution profile for oral thin films of (DCXB 1- DCXB 6)

Accelerated stability study of optimized batch

The ability of a particular formulation in a specific container to remain within its physical, chemical, therapeutic, and toxicological requirements has been defined as a drug's ability to be stable. The object of stability research is to offer proof regarding how a drug substance's or product's quality changes over time while being influenced by various environmental conditions, including temperature, humidity, and light. It is necessary to determine suggested storage conditions, re-test intervals, and shelf lives[21]. The stability test requirements for drug registration application submission in the European Union, Japan, and the United States of America are described in the International Conference of Harmonization (ICH) Guidelines titled, 'Stability testing of New Drug substance and products'(QIA). The length of study and storage conditions were specified by the International Conference of Harmonization (ICH) as follows:

Long-term testing: -25^{0}C/60%RH±5% for 12 months.

Accelerated testing: -40^{0}C ±2^{0}C/75% RH ±5% for 6 months.

Accelerated stability studies were carried out at 40^{0}C/ 75% RH for the best formulations for 1 month.

Method: After being kept at 40±2^{0}C/75±5% RH for a month, the accelerated stability of the best formulation[22] was evaluated in terms of their appearance, *in-vitro* disintegration time, surface pH, and drug release characteristics (Table 4).

Table 4. Results of Accelerated stability study

Batch	**Appearance**	**Folding Endurance**	**Disintegration time (Sec)**	**Tensile Strength (gm/cm^2)**	**% Drug Content**
Initial	Colourless	257±0.33	43±1.10	1.475±0.065	97.23±0.34
After1 month	Colourless	259±0.26	41±1.07	1.263±0.043	96.22±0.12

Using different polymers such as PVP K30 and Propylene glycol in varying percentages, six distinct formulations (DCXB1, DCXB2, DCXB3, DCXB4, DCXB5, DCXB6) of fast-dissolving oral films for Valdecoxib were prepared. All six of the formulas were evaluated to have produced profound results

based on the evaluation parameters. Based on the *in vitro* disintegration time formulation DCXB6 was found to be promising and showed a disintegration time (41±1.07 sec). The optimum formulation was examined for their accelerated stability concerning their appearance, *in-vitro* disintegration time, surface pH and drug release characteristics after storing them at 40 ± 2^0 C / 75 ± 5% RH for 1 month(Table 5).

Table 5. *In-vitro* drug release profile of DCXB6 batch after accelerated stability study

Time (Min)	Initial	After 1 month
5	22.07%	19.06%
10	39.85%	36.43%
15	58.76%	56.01%
20	70.83%	67.35%
25	86.11%	83.54%
30	97.23%	94.18%

CONCLUSION:

Oral films are viewed as a highly promising and essential drug delivery technique nowadays because of their quick disintegration, and better dissolving qualities, especially with paediatric and elderly patients. Even though oral drug delivery systems (ODTs) make up the majority of today's formulations, oral films have become more popular due to their portability, increased patient compliance, and simplicity of use. Both the oral and buccal routes can be used to administer them. They can be used for breath refreshing in addition to being medical films (local anaesthetics, vitamin supplements, and cold allergy remedies). The majority of pharmaceutical companies are being developed by the technology's rapid growth to create oral films for a variety of active pharmaceutical components.

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CONFLICT OF INTEREST

The authors declared that they have no conflict of interest.

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