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(RESEARCH ARTICLE)

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To prepare and evaluate orodispersible tablet of anti-inflammatory drug

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Abstract

Oral drug delivery remains the preferred route for administration of various drugs. Recent developments in the technology have prompted scientists to develop orally disintegrating tablets (ODTs) with improved patient compliance and convenience. Orodispersible tablets are solid unit dosage forms, which disintegrate or dissolve rapidly in the mouth without chewing and water. Orodispersible tablets provide an advantage particularly for pediatric and geriatric populations who have difficulty in swallowing conventional tablets and capsules. This review describes the various formulation aspects, disintegrant employed and technologies developed for ODTs, along with various excipients, evaluation tests, marketed formulations, and drugs explored in this field.

Keywords: Oral dosage form; Oral dispersible tablet; Anti-inflammatory drug

1. Introduction

1.1 Orodispersible Tablets

Tablet is the most popular among all dosage forms existing today because of its convenience of self-administration, compactness and easy manufacturing. Many patients find it difficult to swallow tablets and hard gelatin capsules and do not take their medication as prescribed. It is estimated that 50% of the population is affected by this problem which results in a high incidence of non-compliance and ineffective therapy. The difficulty is experienced in particular by pediatric and geriatric patients, but it also applies to people who are ill in bed and to those active working patients who are busy or traveling, especially those who have no access to water [1].

In an effort to develop drug products that are more convenient to use and to address potential issues of patient compliance for certain product indications and patient populations, recent developments in technologies have come out with Orodispersible tablets (ODT) that can be ingested simply by placing them on the tongue. ODT is a solid dosage form that dissolves or disintegrates within a minute in the oral cavity without the need of water and has a pleasant taste. ODT is also known as mouth dissolving tablet, fast-dissolving tablet, fast-melting tablet, mouth melting tablet or fast-disintegrating tablet [2].

Fast disintegrating dosage form has been successfully commercialized and the growing importance was highlighted recently when the European Pharmacopoeia adapted the term 'Orodispersible Tablets' as a tablet to be placed in the mouth where it disperses rapidly before swallowing [3].

ODTs are designed to disintegrate or dissolve rapidly on contact with saliva, thus eliminating the need for chewing the tablet, swallowing an intact tablet, or taking the tablet with water. Although no water is needed to allow the drug to disperse quickly and efficiently, most technologies utilize the body's own salivation. This mode of administration was

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initially expected to be beneficial to pediatric and geriatric patients, to people with conditions related to impair swallowing, and for treatment of patients when compliance may be difficult (e.g. psychiatric disorders). ODT has previously been distinguished as a separate dosage form because of the specific, intended performance characteristics of such products, which are rapid oral disintegration in saliva with no need for chewing or drinking liquids to ingest these products [4].

1.1.1 Need To Formulate Orodispersible Tablets

The need for non-invasive drug delivery systems continues due to patient's poor acceptance and compliance with existing delivery regimes, limited market size for drug companies and drug uses coupled with high cost of disease management. [5] ODT is one such dosage form which is useful for

- Geriatric patients mainly suffering from conditions like hand tremors and dysphasia.
- Pediatric patients who are unable to swallow easily because their central nervous system and internal muscles are not developed completely.
- Traveling patients suffering from motion sickness and diarrohea that do not have easy access to water.
- Patients with persistent nausea for a long period of time are unable to swallow.
- Especially cancer patients after taking their chemotherapy are too nauseous swallow the H_2 blockers, which are prescribed in order to avoid gastric ulceration.
- Mentally challenged patients, bedridden patients and psychiatric patients.

1.1.2 Advantages of Orodispersible Tablets

Most benefits of ODT are for pediatric, geriatric, and bedridden or developmentally disabled patients. Patients with persistent nausea who are traveling or who have little or no access to water are also good candidates for ODTs. [5].

The major advantage of the ODT formulation is that it combines the advantages of both liquid and conventional tablet formulations, while also offering advantages over both traditional dosage forms[7]. It provides the convenience of a tablet formulation, while also allowing the ease of swallowing provided by a liquid formulation.

- Rapid onset of action and may offer an improved bioavailability.
- Easy to administer in patients having difficulty in swallowing
- Useful for pediatric, geriatric and psychiatric patients
- Suitable during traveling where water may not be available.
- Free of need of measuring the dose, an essential drawback in liquids. So accurate dosing as compared to liquids can be achieved
- New business opportunities

2. Material and methods

Drug celecoxib was obtained as a gift sample from Emcure pharmaceuticals Ltd. Mannitol, sodium starch glycolate, PVP, Magnesium stearate, saccharin sodium and menthol were obtained from Qualigens fine chemicals.

2.1 Preformulation Parameters

2.1.1 Organoleptic evaluation

Colour / Odour

A small quantity of drug was taken on a butter paper and it was analyzed for identification of colour and odour by visual inspection in light.

Melting Point

Melting point is defined as a temperature at which drug gets converted from solid form to liquid form. It is determined mainly by two methods: Capillary tube Method (Fusion Method) and through Melting point apparatus. The melting point was determined by fusion method. A capillary tube was taken which was sealed at one end, and then filled with small amount of drug sample. The capillary tube was inserted into melting point apparatus along with thermometer. Switch on the apparatus and wait till drug sample gets melted. Record the temperature at which it was recorded.

Solubility Analysis

Solubility parameter is the property of a solid, liquid or gaseous chemical substance called solute to dissolve in a solid, liquid or gaseous solvent. The solubility of a substance mainly depends on the physical and chemical properties of the solute and solvent as well as on temperature and pressure of the solution.

Table 1 Solubility Profile according to BP

S.NO.	Description term	Part of solvent required for part of solute
1.	Very Soluble	Less than 1 ml
2.	Freely Soluble	From 1ml to 10 ml
3.	Soluble	From 10ml to 30ml
4.	Sparingly Soluble	From 30ml to 100ml
5.	Slightly Soluble	From 100ml to 1000ml
6.	Very Slightly Soluble	From 1000 to 10000
7.	Practically in soluble	From 10000 or more

- Procedure

Take a small amount of drug in a test tube. Then check its solubility in different solvents like distilled water, 0.1N HCl, 0.1N NaOH, ethanol, methanol, phosphate buffer pH 7.2 & 6.8.

2.2 Determination of Absorption Maxima of Celecoxib

2.2.1 Preparation of Phosphate buffer pH 7.2

34 gm of potassium dihydrogen phosphate were dissolved in 1000ml to produce phosphate buffer of pH 7.4.

2.2.2 Spectrophotometric estimation of Celecoxib

Celecoxib was analyzed quantitatively by UV spectrophotometer in Phosphate buffer pH 7.2. Standard calibration curve was plotted between concentration and absorbance.

2.2.3 Preparation of standard curve of Celecoxib in phosphate buffer pH 7.2

Weigh 100 mg of drug and dissolve in 100ml of phosphate buffer solution pH 7.2. Pipette out 1ml of stock solution and dilute to 100ml of phosphate buffer solution (Sub stock solution). Then pipette out 0.1ml, 0.2ml, 0.3ml, 0.4ml, 0.5ml from sub stock solution and dilute up to 10ml to prepare 1 µg/ml, 2 µg/ml, 3 µg/ml, 4 µg/ml and 5 µg/ml solution. Then absorbance is recorded using UV spectrophotometer at ƛ max 286nm.

2.2.4 Determination of Drug Excipients Incompatibility by FT-IR Spectroscopy

Infra red spectra were recorded by mixing powdered drug with dry powder potassium bromide. FT-IR spectra of the selected formulations were taken and compared with the spectrum of pure drug. The characteristic peaks of drug were obtained by scanning in the range of 400-4000 cm-1 by using the spectrometer (Bruker-α-T, Germany). FT-IR is a technique used to determine the chemical interaction between drug and polymers.

3. Evaluation of flow property of powder

3.1 Precompression parameters

3.1.1 Angle of repose

Angle of Repose was determined using funnel method. The blend was poured through a funnel that can be raised vertically until a specified cone height (h) was obtained. Radius of the heap (r) was measured and angle of repose (θ) was calculated using the formula

$$Tan\theta = h/r$$

Where,
θ is Angle of Repose;
h is height of cone;
r is radius of cone

Table 2 Angle of repose as an indication of powder flow properties

Angle of Repose(o)	Type of Flow
<25	Excellent
25-30	Good
30-40	Passable
>40	Very poor

3.1.2 Bulk density and tapped density

Powder was poured gently through a glass funnel into a graduated cylinder. The cylinder was then tapped from a height of 2.0 cm. until the time when there was no more decrease in the volume. Bulk density and Tapped density was calculated.

Bulk density = weight of sample in g/final volume in cm3 tof the sample contained in cylinder

Tapped density = weight of sample in g/final volume in cm 3 after tapping in the cylinder

3.1.3 Carrs compressibility index

It is used for compare the bulk density.

Carrs compressibility index = tapped density- bulk density /tapped densityX100

3.2 Tablet Preparation

Powder were sifted the compressed by single station different batches were further prepared by varying the concentration ratio if polymers and effect on response was studied.

Table 3 Preparation of placebo with different conc. of polymer

Placed code	P1 (% W/W)	P2 (% W/W)	P3 (% W/W)
Mannitol	93.8	92.55	90.2
Sodium starch glycolate	4	6	8
PVP	0.89	0.89	0.89
Saccharine sodium	0.53	0.53	0.53
Magnesium stearate	0.26	0.26	0.26
Menthol	0.26	0.26	0.26

- Conclusion

By following above mentioned method optimized polymer concentration and ratio were determined and it was concluded that the best result was obtained when we took the polymer concentration as used in formulation code p3 placebo formulation with drug .[6]

Table 4 Preparation of optimized formulation F with drug

S.NO.	Ingredient	F1	F2	F3	F4	F5	F6
1.	Celecoxib	26.84	26.84	26.84	26.84	26.84	26.84
2.	Mannitol	63.4	62.4	61.4	60.4	59.4	58.4
3.	SSG	8	7	6	8	7	6
4.	PVP	0.89	0.79	0.69	0.59	0.79	0.69
5.	Magnesium stearate	0.26	0.26	0.26	0.26	0.26	0.26
6.	Saccharine sodium	0.53	0.53	0.53	0.53	0.53	0.53
7.	Menthol	0.26	0.26	0.26	0.26	0.26	0.26

4. Evaluation of tablets

4.1 Weight variation

Prepared sample of 20 tablets were taken and their average weight were determined than variation was calculated for all 20 tablets and then it was matched the specification in the pharmacopoeia.

4.2 Hardness and friability:

Hardness and friability: hardness and friability of tablets were measured by Monsanto hardness tester: Friability a pre weight tablets sample was placed in friabiltor which is then operated for rpm for mintutes . Compressed tablets theat lose less than 0.5-1.0%of their weight are generally considered as acceptable.[7]

4.3 Content uniformity

Ten randomly selected tablets were weighed and powdered in a glass mortar pestle. The weight equivalent to 10 mg Celecoxib was weighed and dissolved in 5 ml of methanol in volumetric flask using glass stirrer, the volume was adjusted to 100 ml with Sorenson's buffer (pH 6.8) and the solution was filtered. An aliquot of 1.0 ml of solution were diluted to 10 ml Sorenson's buffer (pH 6.8) in separate volumetric flask. The content was determined spectrophotometrically at 251.6 nm.

4.4 Modified disintegration test

For measurement of disintegration time, a petridish (10 cm diameter) was filled with 10 ml of Sorenson buffer pH 6.8. The tablet was carefully put in the center of petridish and the time for the tablet to completely disintegrate into fine particles was noted.

4.5 Wetting time

The method was followed to measure tablet wetting time. A piece of tissue paper (12 cm X 10.75 cm) folded twice was placed in a small Petri dish (ID = 65 cm) containing 6 ml of Sorenson's buffer (pH 6.8), A tablet was put on the paper, and the time for the complete wetting was measured. Three trials for each batch were performed and the standard deviation was also determined.

Figure 1 *In vitro* wetting property

4.6 *In vitro* dispersion time

In vitro dispersion time was measured by dropping a tablet in a glass cylinder containing 6 ml of Sorenson's buffer (pH 6.8). Three tablets from each formulation were randomly selected and *in vitro* dispersion time was performed.

4.7 In *vitro* dissolution studies

In vitro dissolution studies of formulation were carried out using of fresh medium, which was prewarmed at same condition was replaced into the dissolution USP paddle method at 50 rpm in 900 ml of Sorenson's buffer (pH 6.8) as dissolution media, maintained at 37±0.5 ℃. 5 ml of aliquot was withdrawn at the specified time intervals, filtered through whatmann filter paper and analyzed spectrophotometrically at 251.6 nm. An equal volume media after each sampling to maintain the constant volume throughout the test.[8]

5. Results and discussion

5.1 Organoleptic evaluation

The drug was found to be creamish amorphous powder. The melting point of drug was found to be 225 ℃ – 227 ℃. The drug does not have any obnoxious odour.Celecoxib is soluble in phosphate buffer pH 7.2, it is slightly soluble in water, ethanol, and methanol. It is very slightly soluble in 0.1N HCl. It is sparingly soluble in 0.1 N NaOH.

5.1.1 Determination of Absorption Maxima of Celecoxib

Calibration curve of Celecoxib in phosphate buffer pH 7.2

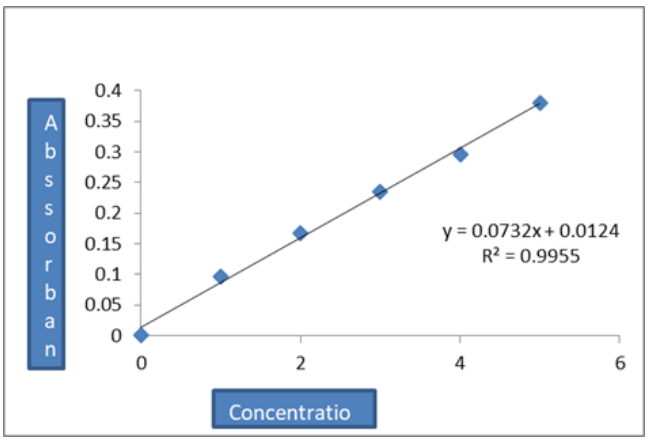

Figure 2 Calibration curve of Celecoxib

Table 5 Concentration and absorbance data for calibration curve of celecoxib

S. No	Concentration (µg/ml)	Absorbance (at 286nm)
1	0	0
2	1	0.092
3	2	0.150
4	3	0.225
5	4	0.276
6	5	0.360

5.2 FT-IR studies

Drug-excipients compatibility study was performed by FTIR technique. The IR spectra of the solution were taken, which indicate no interaction between Celecoxib and polymers was observed [9].

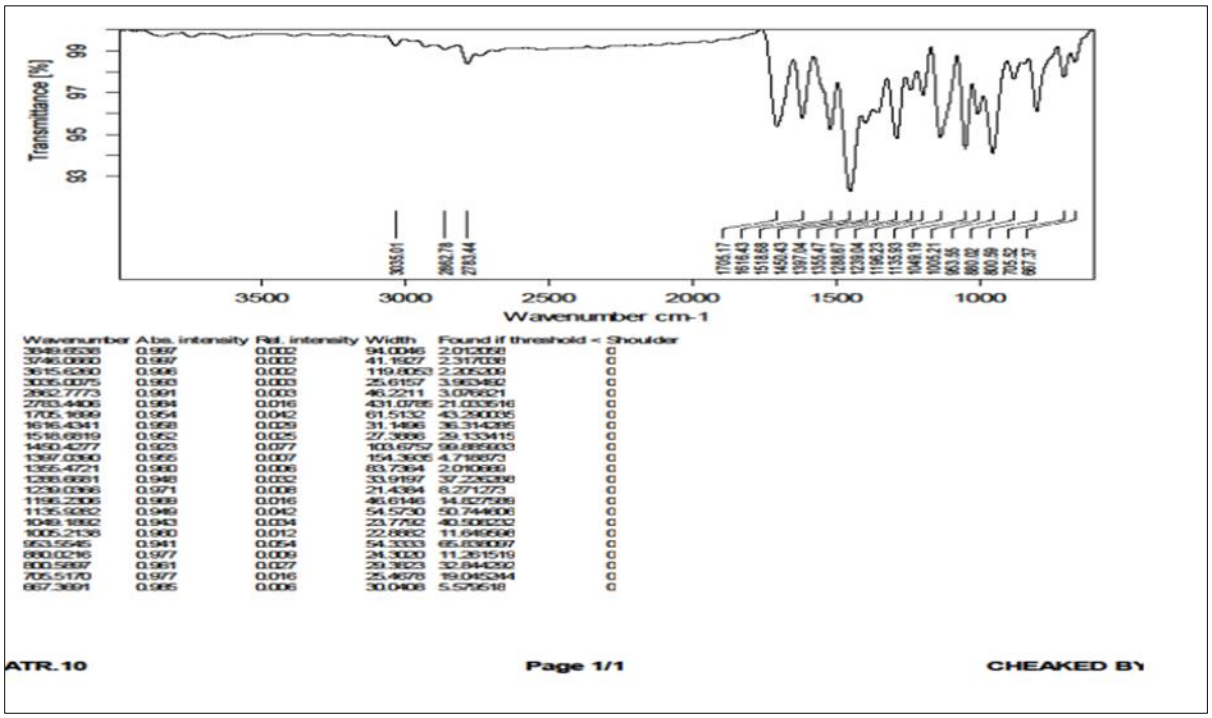

Figure 3 FT-IR Studies

Table 6 various evaluation parameters of formulation batches

Formulation	Weight variation(mg)	Thickness (mm)	Hardness (kg/cm²)	Friability (%)	Drug content (%)
F1	151.4±0.79	2.25±0.04	3.20±0.08	Pass	99.40±0.09
F2	148.2±0.14	2.20±0.12	3.43±0.10	Pass	99.01±0.07
F3	152.3±0.16	2.27±0.09	3.32±0.13	Pass	99.25±0.12
F4	150.4±0.64	2.21±0.17	3.12±0.06	Pass	99.3±0.15
F5	148.5±0.22	2.19±0.13	3.25±0.09	Pass	99.61±0.12
F6	149.8±0.30	2.22±0.07	3.31±0.12	Pass	99.34±0.07

5.3 Hardness

The hardness of prepared formulation is shown in Table: 3. The hardness for orodispersible tablets of each formulation of celecoxib was in the range of 3.12±0.06 to 3.43±0.10 kg/cm2. This ensures good handling characteristics of tablets. (Monsanto hardness tester Rolex India) [10]

5.4 Thickness

The thickness of prepared formulation is shown in Table: 9. the thickness of orodispersible tablets of each formulation of celecoxib was in the range of 2.20± 0.12 to 2.27±0.09mm. This ensures good handling characteristics of tablets.

5.5 Weight variation

The weight variation of the prepared formulation is shown in Table: 9. The weight variation of orodispersible tablets of each formulation of celecoxib was found in the range of 148.2±0.14 to 152.3±0.16 mg; indicating that the weight variation of prepared formulations is within the acceptable limits.(Jyoti scientific industries Gwalior India) [11]

5.6 Friability

The friability of prepared formulation is shown in The percentage friability of orodispersible tablets of each formulation of celecoxib was found in the range PASS; indicating that the friability of prepared formulations is within the acceptable limits and tablets are mechanically stable. (Friability test apparatus, Khera instrument PVT, LTD India.)

5.7 In *vitro* disintegration time

The orodispersible tablets of each formulation of celecoxib got disintegrated rapidly within 15 seconds to 3minutes. Due to use of superdisintegrants there was fast disintegration. As a result patients will get relief from pain as soon as possible.[12]

5.8 In *vitro* drug release

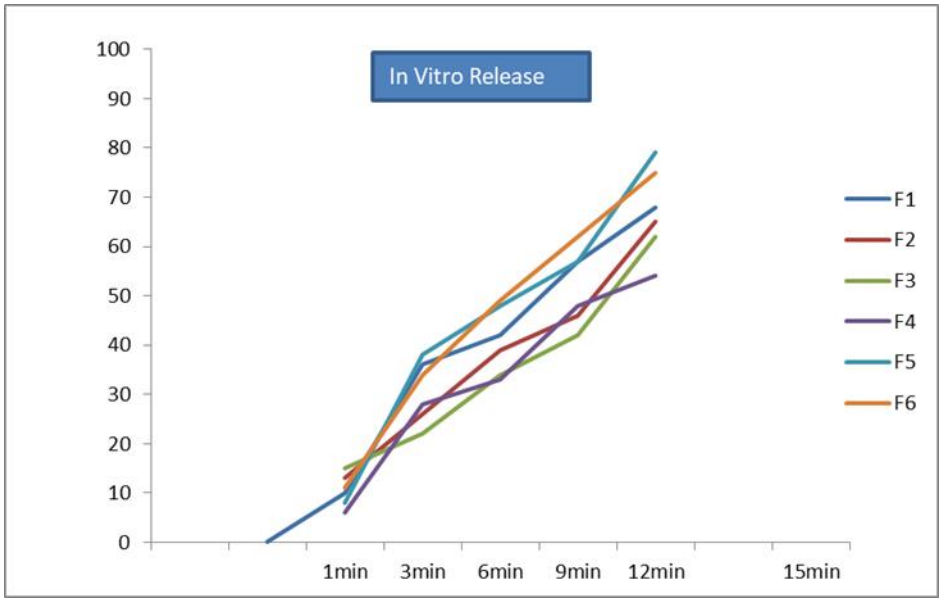

Figure 4 *In vitro* drug release of different batches

6. Conclusion

The oral route of drug administration is the prominent route of drug administration because of ease of access and patient compliance. However, the route is disadvantageous for drugs which undergo significant first-pass metabolism and acid hydrolysis.

The orodispersible tablet were prepared using direct compression method by taking sodium starch glycolate as superdisntegrant plus PVP as a binding agent.it was calculated that ODS doses from proves its singnificant increasing bioavailability of water insoluble drug by increasing its dissolution and solubility as well as therapeutic effect of drug . it also avoid first pass metabolism of drug.

Not only above mentioned parameter indicate its orodispersible formulation is best but all the evolution done also shown orodispersible formulation of celecoxib can be the promising formulation to get good therapeutic effect and potent compliance.

Compliance with ethical standards

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Disclosure of conflict of interest

There is no interest of conflict in this manuscript.

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