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FORMULATION, DEVELOPMENT AND OPTIMIZATION OF CAPECITABINE TABLET DOSAGE FORM AND IN VITRO EVALUATION OF PHYSICOCHEMICAL PROPERTIES

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ABSTRACT

Background: Capecitabine is an antimetabolite type analogue utilized as an antineoplastic agent to treat metastatic and highly developed manifestations of breast and colon cancer, frequently in blend with different other options.[1] Capecitabine is a tumor-enacted antineoplastic operator that fits the novel fluoropyrimidine carbamate class. It was soundly outlined as an orally managed forerunner of 5'-deoxy-5-fluorouridine (5'-DFUR).[2] The present study was carried out to develop and optimize various formulations of Capecitabine tablet dosage forms and characterize the drug's physical, chemical, and mechanical characteristics keeping in mind the end goal to pick what different items (Known as excipients) ought to be utilized as a part of the experiment. **Methods:** Development of Capecitabine oral tablet dosage form was done using suitable excipients like Ludipress Ph. Grade, Microcrystalline Cellulose USP (Avicel PH 102), Pregelatinized Starch USP, Sodium Starch Glycolate USP, Lactose Spray Dried, Crospovidone USP, Magnesium Stearate USP, Colloidal Anhydrous Silica BP (Aerosil-200), Purified Talc BP. Four different formulations F-1, F-2, F-3, and F-4 were developed among which F-4 showed acceptable results and showed good comparison with reference and marketed products. **Results:** It was observed that F-4 creates stable tablets with good characteristics. Different parameters of tablet dosage forms like weight variation test, hardness, weight variation test, friability test, disintegration, thickness, and dissolution showed acceptable results. The average hardness of F-4 was 12.7 kp, the average thickness

was 5.41 mm, the friability was 0.02%, the disintegration time was 4 minutes 25 seconds and the average dissolution was 93.16%. Reference standard, RS, and market sample, MS showed drug content 505.32 mg and 494.22 mg whereas F-4 showed 501.82 mg. **Conclusion:** Parameters like thickness, friability, disintegration, and average dissolution showed good results of F-4 compared with the reference standard market sample. Six months of stability studies of F-4 revealed that there was no significant alteration in physical parameters, drug content, and other profiles.

KEYWORDS: Antineoplastic agent, Capecitabine, Breast and colon cancer, Orally administered.

INTRODUCTION

Capecitabine is a fluoropyrimidine carbamate with antineoplastic action. It is an orally given systemic prodrug of 5'-deoxy-5-fluorouridine (5'-DFUR) which is changed over to 5-fluorouracil.[3] Given orally, it is converted via enzyme pathways to 5-fluorouracil (5FU). As these enzymes are found in higher concentrations in the tumor cells, the treatment is targeted. Proven to be at least as effective as intravenous 5-fluorouracil, it is anticipated that Capecitabine will substantially replace traditional 5-fluorouracil in regimens commonly used in colorectal and breast cancer.[4] It is typically an antimetabolite of the pyrimidine class. An antimetabolite is a chemical that restrains the utilization of a metabolite, which is another substance that is a section of a typical metabolic system.[5] Capecitabine is non-cytotoxic in vitro. On the other hand, in vivo, it is consecutively changed over to the cytotoxic moiety, 5-fluorouracil (5-FU), which is further assimilated. Creation of 5-FU is catalyzed especially at the tumor site by the tumor-related angiogenic component thymidine phosphorylase (dThdPase), in this way minimizing the introduction of sound tissues to systemic 5-FU.[6]

Capecitabine is shown for the adjuvant treatment of patients taken after surgery for stage III (Dukes' stage C) colon malignancy, metastatic colorectal disease, and first-line treatment of cutting-edge gastric tumor in a blend with a platinum-based regimen. Capecitabine in mix with docetaxel is demonstrated for the treatment of patients with generally progressed or metastatic breast cancer after the disappointment of cytotoxic chemotherapy.[7] Capecitabine is additionally utilized as monotherapy for the treatment of patients with provincially progressed or metastatic breast cancer after the disappointment of taxanes and an anthracycline-containing chemotherapy regimen or for whom further anthracycline treatment

is not demonstrated.[8] The efficacy and safety of Capecitabine has been demonstrated in several well-controlled studies.

Formulation, development, and study of Capecitabine tablet dosage forms are logically significant for the development of cancer therapy, since Capecitabine is an important anticancer agent for the treatment and palliative care of many cancers.

The tablet dosage form of Capecitabine offers some effective advantages over other dosage forms (capsules, injectables, etc). So the development of Capecitabine in tablet dosage form is necessary as they offer the greatest dose precision and least content variability which is important for cancer chemotherapy drugs. The tablet dosage form is also the lowest cost of all oral dosage forms and also the most stable in various aspects.

There are three systems for tablet fabricating with the decision relying on the dosage and the drug's physical properties, for example, compressibility and flow of the mix.[9]

For the formulation of tablets, the three granulation methods that are commonly used are wet granulation, dry granulation, and direct compression. Capecitabine raw material is commonly hygroscopic and especially to reduce the steps in the manufacturing procedure of this cytotoxic substance dry granulation or direct compression processes can be used.

In vitro, physicochemical testing of tablet dosage form includes testing of tablet thickness, hardness, friability, average weight, disintegration time, dissolution parameter, etc. In pharmaceutics, the pharmaceutical formulation is the procedure in which distinctive chemical substances, including the active ingredient, are consolidated to create a therapeutic item. Formulation studies include preparing a preparation of medication that is both stable and worthy to the patient. Orally administered medications include fusing the medication into a tablet or a capsule. It is critical to admire that a tablet contains a mixed blend of different substances separated from the medication itself, and studies must be completed to guarantee that the medication is compatible with these different substances.[10]

MATERIAL AND METHOD

Materials

All the materials were in analytical grade and no further purifications were required. Capecitabine USP was supplied by Shaanxi King Stone Enterprise Company Limited (Xian City**,** China). The excipients were of pharmaceutical grade and obtained from various sources

like Ludipress and Crospovidone from BASF chemical company (Evionnaz, Switzerland), Microcrystalline cellulose (Avicel PH 102) from Mingtai Chemical Ltd. (Taoyuan Hsien, Taiwan), Pregelatinized starch from Colorcon Asia Pvt. Ltd. (Merchant Square, Singapore), Sodium starch glycolate from Yung Zip Chemical Ind. Co. Ltd. (Taichung, Taiwan), Lactose Spray Dried from DFE Pharma (Goch, Germany), Magnesium stearate from Peter Greven Nederland C.V. (Venlo, Netherland), Colloidal anhydrous silica (Aerosil-200) from Evonik Industries (Mumbai, India) and Purified talc from MERCK KGaA, (Darmstadt, Germany). Coating materials like Opadry II blue (85G50642) and Opadry II white (85G68918) were obtained from Colorcon Asia Pvt. Ltd. (Merchant Square, Singapore).

Proposed formulation of the core tablets

For the preparation of the core tablet, four different formulas were proposed and their physicochemical properties were evaluated to achieve a good, stable, and palatable tablet that will meet all the specifications of tablet properties. All the formulas were 730 gm in batch size and each tablet was 730 mg in weight. So, all the formulas produced 1000 number of tablets per batch. The purposes or functions of all the used ingredients in different formulations are given in Table 1.

Proposed formulations are given below in Table 2 designed as Formulation–1 (F-1), Formulation–2 (F-2), Formulation–3 (F-3), and Formulation–4 (F-4) measured in mg/tablet. All formulations contained a micronized grade of Capecitabine powder.

Table 1: Justification of ingredients used in the formulation.

Name of the ingredients	Function	Recommendation
Capecitabine	Active Ingredient	-----
Ludipress	Tablet Diluent	-----
Microcrystalline cellulose	Tablet Diluent	-----
Lactose spray dried	Tablet Diluent	-----
Pregelatinized starch	Tablet Binder	5 to 20 %
Sodium starch glycolate	Tablet Disintegrant	2 to 8 %, optimum concentration is about 4 %
Crospovidone	Tablet Disintegrant	2 to 5 %
Magnesium stearate	Tablet Lubricant	0.25 to 5.0 %
Colloidal anhydrous silica	Glidant	0.10 to 1.0 %
Purified talc	Glidant	1 to 10 %

Table 2: Proposed four formulations of Capecitabine 500 mg tablet.

Name of materials	F-1 (mg)	F-2 (mg)	F-3 (mg)	F-4 (mg)
Active material				
Capecitabine USP	504.337	504.337	504.337	504.337
Excipients				
Ludipress USP	----	111.963	123.113	113.113
Microcrystalline Cellulose USP	----	36.150	----	----
Lactose Spray Dried USP	170.913	----	----	----
Pregelatinized Starch USP	----	31.000	31.000	31.000
Sodium Starch Glycolate USP	----	31.000	31.000	31.000
Crospovidone USP	36.500	----	----	----
Magnesium Stearate USP	14.600	6.225	15.725	19.725
Colloidal Anhydrous Silica BP	3.650	6.225	12.225	14.225
Purified Talc BP	----	3.100	12.600	16.600
Coating material				
Opadry II Blue (85G50642)	14.600	14.600	14.600	14.600
Opadry II White (85G68918)	14.600	14.600	14.600	14.600
Purified Water[a]	146.000	146.000	146.000	146.000

Note: [a]Solvent does not appear in the final product.

Abbreviations: USP, United States pharmacopoeia; BP, British Pharmacopoeia, F, formulation.

Preparation of core tablets

Tablets were prepared by direct compression method. The granulation methodology mixes one or more powders and produces a granule that will permit the tableting procedure to be unsurprising and will deliver quality tablets inside the obliged tablet-press speed range.[11] Calculated amounts of active ingredients were weighted and manually sieved through 20 mesh screens and taken in a polybag. All of the excipients except Magnesium Stearate, Colloidal Anhydrous Silica, and Purified Talc were sieved into 20 mesh screens mixed with the first polybag, and mixed for 20 minutes manually. Magnesium Stearate, Colloidal Anhydrous Silica, and Purified Talc were sieved into 40 mesh screens and mixed with the first polybag and mix for 20 minutes manually. Finally, mixed granules are compressed into tablets maintained through a compression machine. Microcrystalline cellulose is a filtered, part-of-the-way depolymerized cellulose that happens as a white, scentless, weak, crystalline powder made out of permeable particles. It is financially accessible in distinctive particle sizes and moisture grades that have diverse properties and uses.[12] Ludipress is a progressed, pregranulated item based on lactose monohydrate (filler) and povidone (binder) - the useful segments needed for tablets to a vital extent. It is a prepared-to-utilize, granular excipient for

direct compression of solid oral dosage forms which decreases the tablet manufacturing procedure to a couple of steps. Fantastic flowability, low water ingestion, perfect particle size conveyance, no isolation of active ingredients, and binding ability are the key highlights of this item.[13] Here, Figure 1 shows the overall sequence of processes in the study.

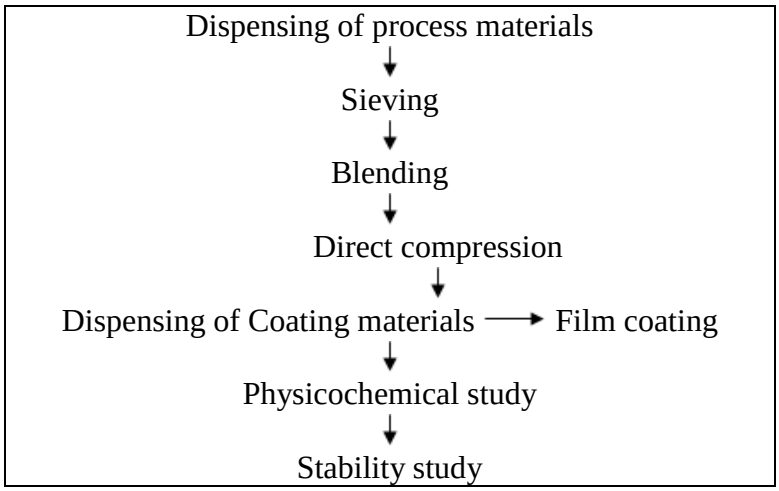

Figure 1: Sequences of the overall study.

Tableting process

The tableting specification of the final blend into the core is shown in Table 3. The machine controlling (IMA Kilian Pressima Tablet Press, Italy) parameters are also specified in Table 4 which signifies overall machine maintenance during the tableting process.

Table 3: Tableting specification of the final blend.

Parameter	Specification
Individual Weight	730 mg ± 4 % (700.8 mg to 759.2 mg)
Mean Weight (10 Tablets)	7.30 gm ± 2 % (7.446 gm to 7.154 gm)
Thickness	5.30 – 5.60 mm
Hardness	Not less than 8 kp
Friability	< 1.0 % w/w
Disintegration Time	NMT 30 min.
Dissolution	NLT 70%
Appearance	White to off-white oblong-shaped

Abbreviations: mg, milligram; mm, millimeter; kp, kilopascal; NMT, not more than; NLT, not less than; min, minute.

Table 4: Machine control (IMA Kilian Pressima Tablet Press, Italy).

Stage	Value (at development stage)
Compression	Thickness: 5.77 mm
	Lower Punch Position: 7.00 mm

	Penetration Depth: 1.2 mm
	Mean Main Pressure: 10.50 KN
Filling cam	6.0 – 9.0 mm
Filling depth	7.50 mm
Feeder speed	5 rpm
Machine speed	9rpm
Tablets per hour	8000 Tablets
Oil lubrication	120 minutes interval

Abbreviations: mm, millimeter; kp, kilopascal; KN, kilonewton; rpm, rotation per minute.

Coating of core tablets

After preparing tablets from the above formulations whose formula meets the optimization level, those are filmy coated with blue-colored Opadry II Blue (85G50642) Ph. Grade and white colored Opadry II White (85G68918) followed by preparing coating suspension with purified water considering 1-2.5% weight gain. Before starting coating, the coating pan is warmed at about 45^{o} C. Table 5 represents the parameters during coating operation which were controlled and maintained as specified.

Table 5: The set parameters range of Thai coater automatic film/sugar coating system coating machine for coating operation.

Parameter	Unit	Set Range
Inlet Air Temperature	^{o}C	70-75
Pan Speed	rpm	7
Spray Gun Atomizing Air Pressure	bar	2
Inlet Damper Position	degree	0
Exhaust Damper Position	degree	30-60
Spray Rate	Gm/min	60-120
Gun Distance From Tablet Bed	cm	15-25

Physicochemical tests of tablets

Various tests were done according to United States pharmacopeia (USP).

A. Infrared Absorption: Bands in the region of 1500-1760 cm^{-1} obtained from the test sample correspond to the brand obtained for Capecitabine.

Test specimen— Fine powder one tablet was created with a mortar & pestle. Mix 1mg of this with 300 mg of potassium bromide.

B. The retention of the significant peak in the chromatogram of the test arrangement relates to that in the chromatogram of the standard preparation, as acquired in the examination.[14]

Not more than 2 of the 20 tablets digress from the normal weight by more than± 7.5% and none by more than ± 15 %.

We checked the hardness of 10 tablets with an Erweka Electronic Hardness Tester (Germany). Calculated and recorded the average hardness of 10 tablets. The thickness of 10 tablets by a suitable slide calipers or thickness tester was calculated and the average thickness of 10 tablets. Twenty tablets were taken and brushed to free any powder. Weighed and recorded the weight of the tablets. At the end of the rotation period remove the tablet from the drum and carefully brush free from adhering powder. Reweighed the tablets and the percentage of loss was calculated with equation[1] in weight as follows:

$$\text{Calculation: } \%\ \text{Loss} = \frac{\text{Final Weight- initial Weight}}{\text{Initial Weight}} \times 100 \quad [1]$$

Erweka disintegration tester (Germany) was used and six tablets were placed into six tubes. Then added disc to each tube & suspended the tubes in a 1000 ml beaker having 800 ml of purified water maintaining the temperature of the water from 36.5^0C to 37.5^0C. 800 ml of water was required to maintain that the wire mesh at its most elevated point was no less than 25 mm underneath the surface of water and the least point is at 25 mm over the base of the measuring glass. Operated the apparatus & recorded the time required for disintegration.

The assay was conducted by using Prominence Shimadzu HPLC (Japan). The column used was a stainless steel section (25 cm × 4.6 mm) stuffed with stationary phase C 18(5 µm) (Octadecyl Silane is appropriate). The flow rate was 1.00 ml/min, the wavelength was 250 nm, the temperature was 40°C, and Inject Volume was 10 µL. Diluent was the mixture of water, methanol & acetonitrile (60**:** 35**:** 5), and Diluted acetic acid was a 0.1% (v/v) mixture of acetic acid in water. The mobile phase was prepared as a filtered and degassed solution of a mixture of methanol, diluted acetic acid & acetonitrile (80**:** 15**:** 5).

We injected separately 10 µl both the Standard Preparation and Sample Preparation into the liquid chromatograph. In the chromatogram obtained from the Standard and Sample Preparation, calculate & measure the responses for Capecitabine peaks. Equation[2] was used to calculate the content of Capecitabine per tablet.

$$\text{Content of Capecitabine / Tab} = \frac{\text{PA X WStd. X 250 X 100 X PStd. X Avg. Wt}}{\text{AStd. X 50 X WS X 5 X 100}} \text{ mg /tab} \quad [2]$$

Here,

AS = Peak area due to Sample Preparation

WStd = Weight taken of Working Standard in mg
PStd = Potency of Working Standard in percentage
AStd = Peak area due to Standard Preparation
WS = Weight of sample in gm

The dissolution was conducted by using Prominence Shimadzu HPLC (Japan) as well. The column was a stainless steel section (25 cm × 4.6 mm) stuffed with stationary phase C 18(5 µm) (Octadecyl Silane is appropriate). The flow rate was 1.00 ml/min, the wavelength was 250 nm, the temperature was 40°C, Inject Volume was 10 µL. Diluted acetic acid was prepared in a 0.1% (v/v) mixture of acetic acid in water. The mobile phase was filtered and a degassed solution of a mixture of methanol, diluted acetic acid & acetonitrile (80: 15: 5) was made.

In the chromatogram obtained from the Standard and Sample Preparation, calculated & measured the responses for Capecitabine peaks. Equation[3] was used to measure the dissolution percentage of the tablet.

$$\text{Dissolution Percentage} = \frac{\text{AS X WStd. X 5 X 900 X 100 X PStd. X 100}}{\text{AStd. X 50 X 100 X 500 X 5 X 100}}\% \quad [3]$$

Where,

AS = Peak area of Sample Preparation
WStd = Weight taken of Working Standard in mg
PStd = Potency of Working Standard in percentage
AStd = Peak area of Standard Preparation

Stability investigation of the optimized formulation was directed at Long-term stability test conditions and accelerated stability test conditions taking after consideration of International Conference on Harmonization (ICH) rules.[15] Accelerated stability condition was 40^{o}C + 2 & 75% RH + 5% and at Long term stability test condition was 30^{o}C + 2 & 65% RH + 5%. The sample was packed in an Alu-alu blister and stored in both conditions in two separate Pharma Tast Stability Chambers (Germany). The test sample was collected at 0,1,3, 6 months intervals from both conditions and tested for Average Weight, Hardness, Disintegration time, Dissolution, and Assay.

RESULTS AND DISCUSSION

Four different formulations were prepared and evaluated for the development of a stable tablet dosage form of Capecitabine USP 500 mg tablet. The direct compression method was targeted because the drug Capecitabine is an anticancer drug and has potential safety issues related to the manufacturing process. Therefore, to reduce the handling or manufacturing steps and to reduce the risk related to cytotoxic drug handling, the direct compression method is selected for the development of the Capecitabine USP 500 mg tablet dosage form with limited health hazards.

The tablets of the proposed formulations were evaluated with different assessment tests like weight variation test, hardness test, weight variation test, friability test, disintegration, and dissolution test.

In the first formulation F-1, the granule was so fine and the percentage of coarse powder was so negligible that it could not compact into stable tablets. This formulation shows extensive sticking and layer separation problems. As a result of the compaction problem, further modifications were considered in the formulation. Second formulation F-2, sticking has been observed in tablets of this formulation. Tablets were not released from the machine properly. Tablets were been attached to the upper punches of the machine. Tablets were not been dispatched from the machine properly. The flow property of the granules was very poor. Granules had to be fed from the hopper using a spatula, bin lifter could not be used due to improper flow of granules. Pregelatinized Starch USP and Sodium Starch Glycolate USP were included instead of Crospovidone USP to solve the compaction problems. To improve the problems from the previous formulation F-3 was developed, to improve production time and to compress within one compression step, Ludipress was added instead of Microcrystalline Cellulose USP (Avicel PH 102). The extra amount of Ludipress was also added to improve the compression process. The amount of Magnesium Stearate USP, Colloidal Anhydrous Silica BP (Aerosil-200), and Purified Talc BP also increased to solve the poor flow property. This formulation shows relatively good flow properties but the sticking problem is still present. For optimization of the formula, further modifications were considered.

Finally, in F-4 extra amount of Magnesium Stearate USP, Colloidal Anhydrous Silica BP (Aerosil-200), and Purified Talc BP were added to solve the existing sticking problem and found satisfactory results. So, the formulation was fixed as stable, and during compression,

the tableting parameters were evaluated at various hardness and weight to adjust the best parameter of the machine to compress a good tablet without any defects.

Figure 2 indicates the different physicochemical reports like hardness, thickness, average weight, friability, disintegration time, and dissolution reports of different formulations (F-1 to F-4).

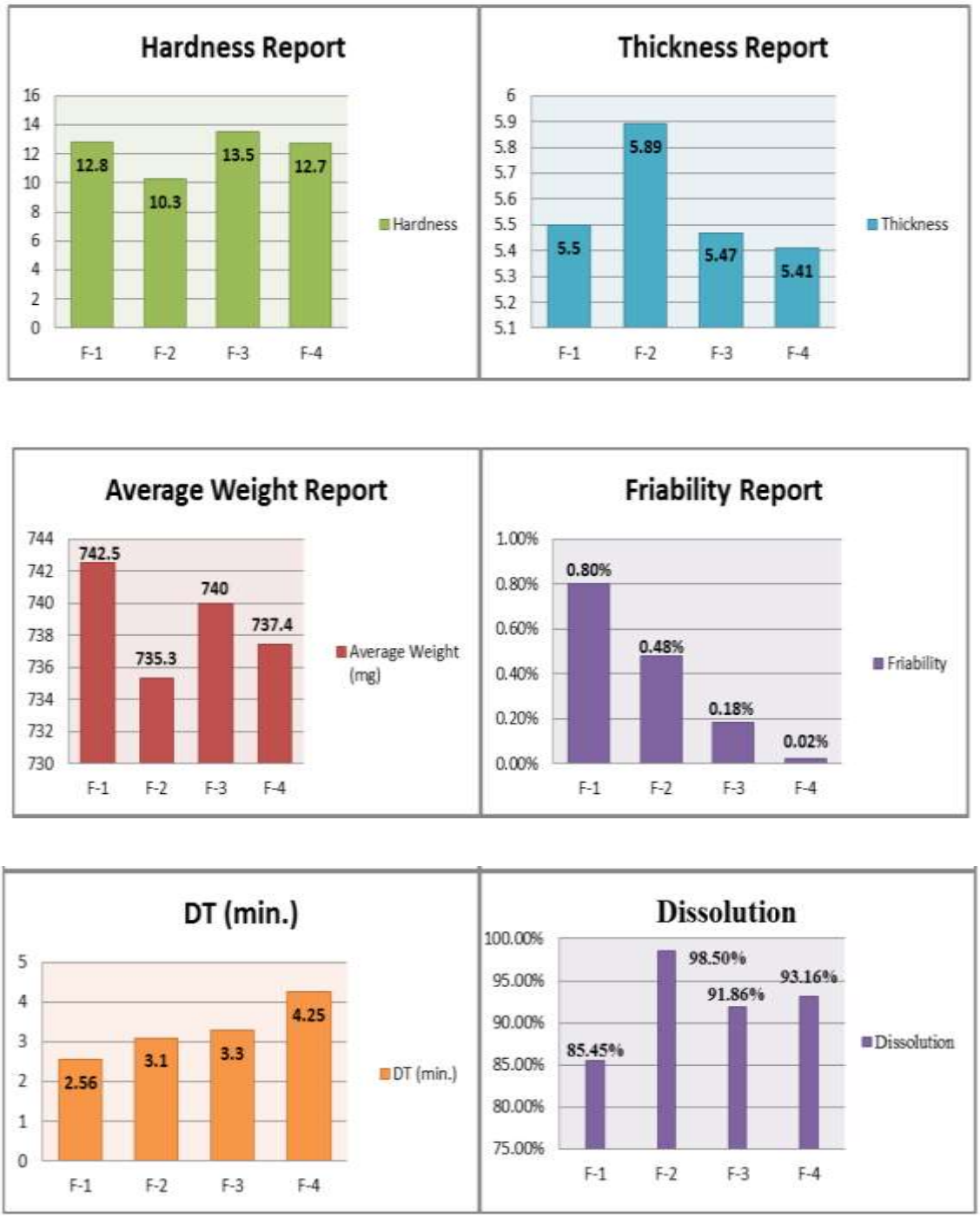

Figure 2: Different analysis reports of four formulations F-1, F-2, F-3 and F-4.

Abbreviation: DT, Disintegration time.

Table 6 shows the different friability results of tablets at different revolutions of the proposed formulation F-4. The friability result of the proposed formulation F-4 met the specification of < 1.0 % w/w.

Table 6: Friability results of tablets from proposed formulation F-4 at different rpm.

No. of tablet	No. of revolution	Initial weight	Final weight	Friability
10	100	7.372	7.352	0.020
10	200	7.372	7.314	0.058
10	300	7.372	7.360	0.120

Percent friability of the proposed formulation F-4 is increased as revolution increased but didn't cross the limit as illustrated in Figure 3.

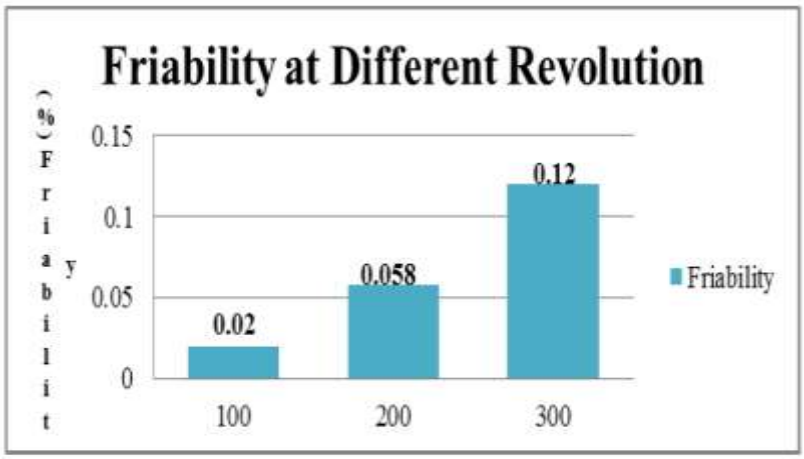

Figure 3: Friability (%) of Proposed Formulation F-4 at Different Revolution.

Dissolution testing is broadly utilized as a part of pharmaceutical testing for the enhancement of formulation and quality control. It is helpful in the pharmaceutical and biotechnology field to form drug dosage forms and to create quality control determinations for its manufacturing procedure.[16] Dissolution is a case of in-vitro test that can be utilized to specify formulations that may represent potential bioequivalence issues.[17] Here, as shown in Table 7, the average percentage of dissolution of six tablets showed good acceptable results.

Table 7: The dissolution (%) of six tablets of proposed Formulation-4.

No. of Sample	Absorbance of Standard	Absorbance of Sample	% of Dissolution	Average	Limit
01.	8661851	8812502	94.12	93.16	Not less than 70%
02.	8661851	8473793	90.50		

03.	8661851	8979850	95.91		
04.	8661851	8472385	90.49		
05.	8661851	9171989	97.96		
06.	8661851	8661851	89.98		

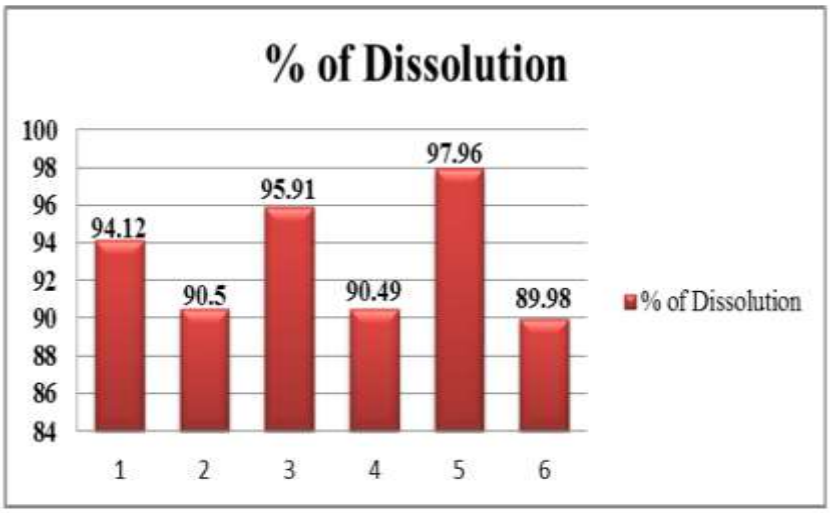

Figure 4: Dissolution (%) of six tablets of proposed formulation F-4.

Figure 4 shows the results of percent dissolution of the six tablets which signifies no remarkable alteration in the dissolution profile.

Rapid, simple, and sensitive spectrophotometric methods can be used for the determination of Capecitabine. The methods are based on their oxidation and precipitation reactions.[18] Table 8 indicates the drug content of the proposed formulation F-4 and Figure 5 shows the drug content measured in Assay-1 and Assay-2 and their average which exhibit acceptable results according to USP specification.

Table 8: Capecitabine content of tablets from proposed formulation F-4.

No. of assay	Capecitabine Content Per Tablet (mg)	Average (mg)	USP Specification
Assay-1	502.74	**501.82**	From 93.0% to 105.0%
Assay-2	500.89		

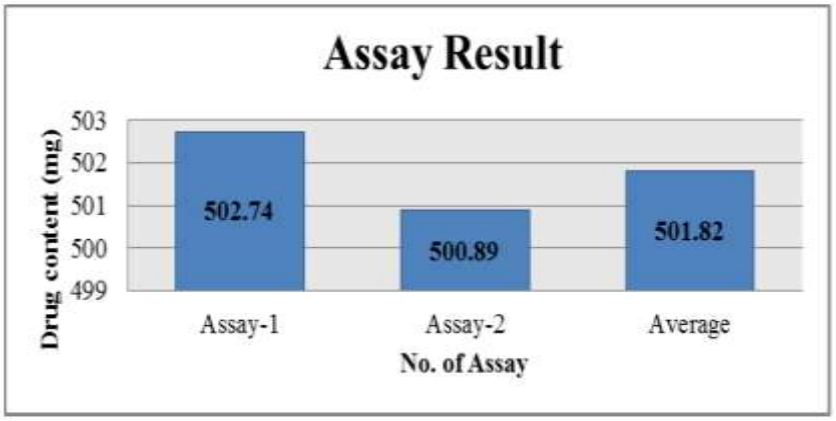

Figure 5: Drug content of tablets prepared from formulation F-4 with average.

Comparison of formulated drug with innovator drug and marketed drug

The formulated tablet was compared with one marketed product and an innovator drug which were collected from two different manufacturers. Available marketed product was denoted as Marketed Sample (MS) & innovator drug was denoted as Reference Standard (RS).

Table 9: Comparison of different parameters between formulation-4 with patent drug and marketed product.

Parameter	F-4	RS	MS
Individual Weight (mg)	737.40	715.30	754.60
Actual Drug Content (mg)	501.82	505.32	494.22
Thickness (mm)	5.53	5.32	5.69
Friability (%)	0.02	0.012	0.089
Hardness (kp)	12.7	10.4	13.4
Disintegration Time (min.)	4.25	5.60	7.30

Abbreviation: RS, Reference Standard; MS, Marketed Sample; F-4, Formulation-4.

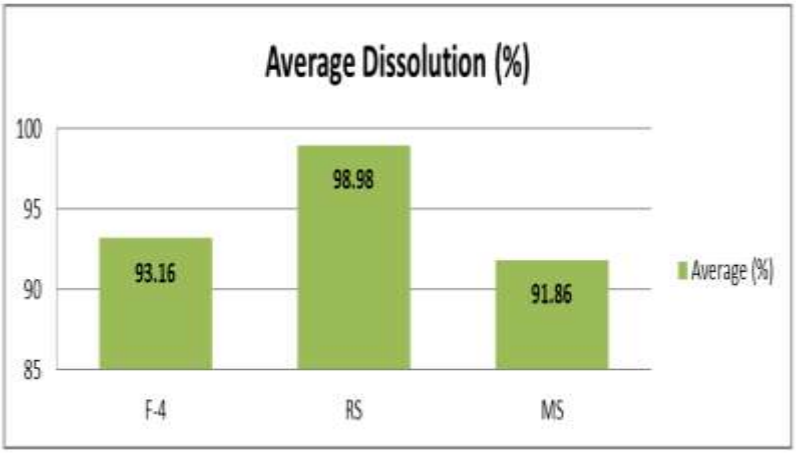

Figure 6: Comparison of average dissolution (%) of F-4 with Innovator and Marketed Sample.

The comparison among patent drug (Reference Standard) and market samples with F-4 in Table 9 also shows acceptable results supporting the formulation. Reference standard and marketed samples showed drug content of 505.32 mg and 494.22 mg whereas F-4 showed 501.82 mg. Other parameters like thickness, hardness, friability, and disintegration time showed good results of F-4 compared with the reference standard and market sample. as shown in Table 9. A comparison of the average dissolution (%) of F-4 with innovator and marketed sample is also shown in Figure 6.

Stability study

The stability studies were carried out at 40^0C ± 2^0C & 75% RH for accelerated conditions in Alu- Alu blister pack according to ICH guidelines. Samples were tested initially and the stability test had been completed up to 06 months at accelerated condition. The stability test had also been completed up to 06 months at long-term conditions at 30^0C ± 2^0C & 65% RH. No significant change in the appearance of the tablet at accelerated conditions and long-term conditions. The potency of the active ingredients is within the limit at both accelerated conditions and long-term conditions. Film coating properties meet the requirements and dissolution results are within the limit at both conditions. Related substances comply with the test of USP and there was no interaction of primary packaging materials with the dosage form found during the study, providing that the Alu-Alu blister pack is suitable and stable for the product.

Table 10 and Table 11 indicate the stability report of Capecitabine Tablet of formulation F-4 in Alu- Alu blister pack in long-term conditions at 30°C & 65% RH and in accelerated conditions at 40°C & 75% RH respectively.

Table 10: Long-term stability study report of Capecitabine Tablet at 30°C & 65% RH.

Parameter	**Test Result**		
Duration	**Initial**	**After 3 Months**	**After 6 Months**
Average Weight	737.40 mg	732.56 mg	720.28 mg
Hardness	12.70 kp	12.27 kp	10.27 kp
Disintegration time	4 min 25 sec	4 min 15 sec	4 min 06 sec
Dissolution	93.16 %	92.30 %	91.82 %
Assay	502.74 mg	495.02 mg	489.79 mg

Table 11: Accelerated stability study report of Capecitabine Tablet at 40°C & 75% RH.

Parameter	**Test Result**		
Duration	**Initial**	**After 3 Months**	**After 6 Months**
Average weight	720.25 mg	726.08 mg	715.50 mg

Hardness	12.40 kp	12.72 kp	10.66 kp
Disintegration time	4 min 05 sec	3 min 45 sec	3 min 50 sec
Dissolution	93.48 %	90.70 %	94.72 %
Assay	500.25 mg	492.08 mg	485.50 mg

From the above tables and figures, it can be said that Formulation-4 was stable and produced good quality Capecitabine USP 500 mg tablets. The average hardness of F-4 was 12.7 kp, the average thickness was 5.41 mm, the friability was 0.02%, the disintegration time was 4 minutes 25 seconds and the average dissolution was 93.16%. Six months of stability studies of F-4 revealed that there was no significant change in physical parameters, drug content, and other characteristics.

The comparison among patent drugs (Reference Standard) and market samples with F-4 also indicated acceptable results supporting the formulation. Reference standard, RS, and market sample, MS showed drug content 505.32 mg and 494.22 mg whereas F-4 showed 501.82 mg. Other parameters like thickness, friability, disintegration, and average dissolution showed good results of F-4 compared with the reference standard and market sample. The stability reports of long-term and accelerated stability studies also supported that the results are suitable for the Capecitabine USP 500 mg tablet formulation and meet all the specifications.

CONCLUSION

The approach of the study was to formulate and develop Capecitabine USP 500 mg tablets and their evaluation of physicochemical properties. The study revealed that the physicochemical properties of the prepared tablets complied with the USP requirements. Direct Compression technique can be used successfully for the preparation of cytotoxic drugs to minimize manufacturing steps and handling. The study tries to develop a stable and acceptable formulation technique for a cytotoxic drug like Capecitabine that is found in Formulation-4 (F-4).

Quality parameters of pharmaceutical products are very important for optimum efficacy and safety. So, it can be concluded that the prepared Capecitabine USP 500 mg tablet maintains quality attributes. The areas where more work can be done include further improvement in various properties like flow property, compaction pattern, etc., and at the same time reduction of the cost of manufacturing through the direct compression process of Capecitabine USP 500 mg tablet dosage form. Another suitable alternative like cost-effective excipients can be used to achieve the goal.

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Disclosure

In this work, there is no conflict of interest.

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