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FORMULATION AND EVALUATION OF ORALLY FAST DISSOLVING WAFER OF ETODOLAC USING NATURAL GUM

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ABSTRACT
Oral Wafers are intended for the application in the oral cavity on the tongue, drug absorbs totally through tongue artery and entered in to systemic circulation. So, they are an innovative and promising dosage form especially for use in pediatrics and geriatrics. Etodolac was selected as the active drug as it has low solubility and it is indicated in to Anti-arthritis where an immediate relief is always needed. The prepared wafers, based on different formulations, were evaluated. A 3^2 full factorial design was used to optimize the film. Natural Gum was found to be a good film forming agent. The concentration of PVP and Grevillea Robusta Gum were selected as independent while % drug release was a dependable variable in the formulation. Formulation F9 was found to be the optimized among all nine batches with 98.26% release. Increased in the levels of PVP K30 causes the decreased in the folding endurance and increased in the % elongation. Surface pH of all the formulation was measured and found in acceptable pH range. DSC spectra of film shown the drug was totally embedded within polymer matrix, so stability of drug was also increased in formulation. Stability study showed that formulation was stable over a period of stability conditions without any unacceptable changes.

KEYWORDS: Etodolac, Solvent Casting, Oral Wafer, Grevillea Robusta Gum**,** PVP K30.

INTRODUCTION
The oral cavity has been investigated as a site for drug delivery for a long period of time. In 1847 Sombrero found that nitroglycerine was absorbed from the oral cavity. Since then various active substances have been investigated for local or systemic use.[1] Oral drug delivery is considered to be an important alternative to the perioral route for the systemic administration of drugs, as it considered the most convenient, easy, safest route for administration.[2] The novel technology of oral fast dissolving dosage forms is known as fast dissolve, rapid dissolve, rapid melt, quick disintegrating tablets. However, the function and concept of all these dosage forms are similar.[3] The most common complaint was swallowing tablets (dysphasia) by surface form and taste. The problem of swallowing tablets was more evident in the pediatric and geriatric patients, as well as travelling patients who may not have ready access to water[17]. Research and development in the oral drug delivery segment has been led to transition of dosage forms from simple conventional tablets/capsules to oral disintegrating tablet (ODT) to wafer to the recent development of oral thin wafers (OTW) can be considered as an ultra-thin strip of postage stamp size with an active agent or active pharmaceutical ingredient (API) and other pharmaceutical excipients. The advantage so of convenience of dosing probability of ODF has led to wider acceptability of dosage form by pediatric as well as geriatric population equally.[2,4]

Liquid formulations prepared for thin wafer casting can be in the form of solutions, emulsions, dispersions or suspensions. Dispersions or emulsions for casting may be prepared as oil-in-water phases and emulsions are typically used for the manufacture of aqueous formulations to which an oil-soluble ingredient, such as flavor may be added. Thin wafer oral dosage form solutions for casting will require the use of ICH class 3 solvents in order to benefit from an acceptable industry safety profile. The drying process is a critical operation and the drying process must assure that the class 3 solvent is removed to acceptable levels provided for by the draft guidelines.[5]

MATERIALS AND METHODS
Material
Etodolac was obtained from Lupin Pharmaceuticals Mumbai, Polyvinyl pyrrolidone K-30 from Evonik Mumbai, Grevillea Robusta Gum locally collated, Mannitol LR Grade from Research-Lab Mumbai, Polyvinyl Alcohol from Reliance, Cellulose, Ethanol and Methanol were obtained from Merck Specialties Pvt, Ltd, Mumbai.

Method

Solvent casting method

Orally Fast Dissolving Wafer of Etodolac was prepared by Solvent Casting Method. In this water soluble polymer was completely dissolved in water to form uniform clear viscous solution; all other ingredients including API were dissolved in a small portion of suitable solvent. This solution was kept for an hour to remove all the air bubbles. This bubble free solution was poured into a suitable glass mold and kept in oven at 40º-50ºC.[6,9,10]

Evaluation of Wafer[7,8,11]

Thickness

Micrometer screw gauge was used at different locations to measure the thickness.

Folding Endurance

The wafer was fold at the same place, the times at which the wafer break was measured.

In Vitro Disintegration Studies

Typical disintegration time for wafer is 5-30seconds and gives an indication about the disintegration and dissolution characteristics of the wafer. The wafer as per the dimensions (3 x 3 cm) required for dose delivery was placed in a petridish containing 10 ml phosphate buffer (pH 6.8). Time required for the wafer to break was noted as in- vitro disintegration time. Petri dish was shaken with hands by giving jerks. This test was performed on three wafer of each formulation and mean standard deviation calculated.

Weight of Wafer

Mouth dissolving oral wafer were weighed on analytical balance and average weight can be determined for each wafer. It was desirable that wafer should have nearly constant weight. It was useful to ensure that a wafer contains the proper amount of excipients and API, useful to ensure that a wafer contained the proper amount of excipients and API.

Tensile Strength

Tensile strength was a maximum stress applied to a point at which the strip specimen breaks. It was calculated by applied load at rupture divided by the cross sectional area of the strip as given in the following equation:

Tensile strength = force at break × 100/ initial cross sectional area of wafer in mm^2

Percent Elongation

When stress was applied to a wafer sample it stretches and this was referred as strain. Strain was basically the deformation of wafer divided by original dimension of the sample. Generally elongation of wafer increases as the plasticizer content increases.

% Elongation = Increase in length× 100/ Initial length of wafer

Drug Content Uniformity

It determined by any standard assay method described for the particular API in any of the standard pharmacopoeia. Content uniformity was determined by estimating the API content in individual strip. In which the wafer was placed in the 100 ml phosphate buffer 6.8. The absorbance was measured in the limit of content uniformity is 85-115%.

Surface pH

The wafer to be tested was placed in a Petri dish and was moistened with 0.5 ml of distilled water and kept for 30 sec. The pH was noted after bringing the electrode of the pH meter in contact with the surface of the formulation and allowing equilibration for 1 min and an average of three determinations for each formulation was done.[12]

In Vitro Dissolution Studies

Dissolution is defined as the amount of drug substance that goes into the solution per unit time under standardized conditions of liquid/solid interface, temperature and solvent concentration. The standard paddle apparatus described in any of the pharmacopoeia can be used for dissolution testing. The selection of dissolution medium will essentially depend as per the sink conditions and highest dose of API. The temperature of dissolution medium should be maintained at 37 ± 0.5°C and rpm at 50.[13,14,15]

Stability Studies:[16,17,18,19,20].

The standard test conditions for stability study given in Table 1.

Table 1. Test conditions for stability study.

Test Conditions	
Duration of study:	180 days
Temperature conditions:	40± 2°C
Relative humidity conditions:	75± 5%

The Optimized formulation was evaluated mainly for its physical characteristics at the predetermined intervals like appearance (colour changes), pH and drug content and disintegration time.

Table 2 Variables in optimization study.

Variables	**Factor**
Independent	
X1	**Grevillea Robusta Gum**
X2	**Polyvinyl Pyrrolidone K-30**
Dependent	
Y1	**Release (%)**

Table 2. Ranges of independent variables used in factorial design.

Formulation code		Coded Values		
	X_1	mg	X_2	mg
F1	-1	10	**-1**	30
F2	0	20	-1	30
F3	+1	30	-1	30
F4	-1	10	0	40
F5	0	20	0	40
F6	+1	30	0	40
F7	-1	10	+1	50
F8	0	20	+1	50
F9	+1	30	+1	50

Table 3. Compositions of formulations using 3^2 factorial design.

Composition / Form. Code	Etodolac (mg)	GR Gum (mg)	Polyvinyl pyrrolidone K-30 (mg)	Polyvinyl alcohol (mg)	Mannitol (mg)	PEG 400 (mg)
F1	60	10	30	30	8	4
F2	60	20	30	30	8	4
F3	60	30	30	30	8	4
F4	60	10	40	30	8	4
F5	60	20	40	30	8	4
F6	60	30	40	30	8	4
F7	60	10	50	30	8	4
F8	60	20	50	30	8	4
F9	60	30	50	30	8	4

RESULT AND DISCUSSION

1. Mechanical properties

A. Tensile strength

From the results it cleared that when the concentration of the polymer increased, the tensile strength of the wafer also increased. The formulation F8 showed the maximum tensile strength. Presence of natural gum as a wafer forming polymer imparted the flexibility to the Wafer. Tensile strength measured the ability of the wafer to with stand rupture. The formulation F8 showed the maximum strength 1.6175 ± 0.02475 as in Table 5. This might be due to formation of strong hydrogen bonds between polymer and superdisintegrant thereby imparting flexibility to withstand rupture, but formulation F9 also showed comparable tensile strength as compared to F8 formulation.

B. Percentage elongation of the wafers

The wafer of 3cm x 3cm was taken for the studies. Percentage elongation was found to be increased as increase in concentration of polymer in the wafer and reported in table 4.

2. Thickness the wafer

The thickness of the drug loaded wafers F-1 to F-9 formulations was measured with the help of micrometer screw gauge at different strategic locations like four corners and center of the each wafers and mean standard deviation calculated. Wafer thickness should be controlled within a ± 5% variation of standard value. This was essential to assure uniformity in the thickness of the film as it was directly related to the accuracy of dose and other mechanical properties of the wafer. Thickness of a single wafer varies from 0.07±0.017 to 0.10±0.008 mm and reported in the Table 4.

3. Weight variation of wafer

The weight of each wafer strip was taken on Electronic analytical balance and the weight variation was calculated. Weight variation varies from 62±1.224 to 70.8± 1.643 and results given in the Table 4.

4. Folding endurance of the wafers

The number of times the wafer fold until it broke. The studies reflex the influence of concentration of PVP K30 in the formulation as the concentration of PVP K 30 was increased, folding endurance was also increased. Formulation F1, F2 and F3 showed the largest folding endurance. Folding endurance of all Etodolac oral wafers reported in Table 5.

5. Surface pH

Surface pH of the formulations did not showed considerable variations in pH. All formulations showed acceptable pH range 6.08-7.43. This study also reflected the influence of concentration of PVP K 30 in the formulation and there was increase in proportion of PVP K30 showed in the table no.5

6. In-vitro disintegration test

In-vitro disintegration time was determined visually in a glass dish of 25 ml distilled water with swirling every 10 seconds. The disintegration was the time when wafer broke or disintegrated. Superdisintegrants should be

incorporated in the wafer formulation to improve disintegration rate. PVP K30 was incorporated as a superdisintegrant and all the wafers were subjected to disintegration test and results obtained. The invitro disintegration time of all Etodolac wafers reported in Table 4. The studies showed that as there was increased in concentration of PVP K30, disintegration time of the wafer decreased.

8. In-vitro drug release study

In-vitro dissolution study showed maximum release i.e. 98.26% for F9 formulation this could be attributed to higher concentration of PVP and GR Gum in the formulation and in-vitro drug release data shown in Table 6.

9. Optimization

Statistics was applied to the results obtained from general factorial design in which two independent variables varied namely GR Gum (X1) and polyvinyl pyrrolidone (X2) and their effect is recorded on dependent variable namely % drug release (Y1).

Evaluation and interpretation of research findings are almost important and the p-value serves a valuable purpose in these findings. Table 8 shows ANOVA for the dependent variable % drug release.

The values of X_1 and X_2 were found to be significant at $p < 0.0046$, hence confirmed the significant effect of both the variables on the selected responses. Variable caused significant change in the responses. From this data optimum concentration of polyvinyl pyrrolidone 450 mg and gum 270 mg was found.

The Variance Inflation Factor (VIF) measured how much the variance of that model coefficient was inflated by the lack of orthogonally in the design and was calculated for % drug release. It was found to be near to one which indicating good estimation of the coefficient. Similarly Chi-squared was near to zero which led to good model. The values of Prob>F were less than 0.0046, which indicated model terms were significant.

The linear model obtained from the regression analysis used to build a 3-D graphs in which the responses were represented by curvature surface as a function of independent variables. The relationship between the response and independent variables can be directly visualized from the response surface plots.

The response surface plots were generated using Design Expert 8.0.4 software presented in figure.3 to observe the effects of independent variables on the response studied % drug release. From response surface 3 level factorial designs was chosen using linear design mode. The range was set from minimum 75.01 to maximum 98.26. The 9 run was performed for the response % drug release and model was found to be linear.

10 Uniformity of content

Drug content of optimized batches are calculated by using wafer containing 180 mg of Etodolac. Three trials from each formulation are analyzed spectrophotometrically. The mean value and standard deviation of all the formulations are calculated. The drug content ranging from 92.03±0.01575 to 98.7±0.05217. The results indicated that in all the formulations the drug content is uniform. The studies also show that uniformity of content is within the specifications range 85-115% and results shown in Table 5.

Table 4. Evaluation Parameter of Formulation.

Characteristic	Tensile Strength(kg/mm^2) Mean ± SD	Percent Elongation (%) Mean ± SD	Thickness(mm) Mean ± SD	Weight (mg) Mean ± SD
F1	0.9914 ± 0.001682	26.66 ± 0.1732	0.08 ±0.015	62 ±1.224
F2	1.0129 ± 0.01055	35.33 ± 0.1529	0.08 ±0.019	63.6 ±0.894
F3	1.0736 ± 0.01331	30 ± 0.1000	0.10 ±0.008	63.8 ±1.264
F4	1.1414 ± 0.05692	45.55 ± 0.0583	0.07 ±0.020	67.4 ±0.894
F5	1.2451 ± 0.03002	43.33 ± 0.2549	0.08 ±0.008	70.8 ±1.643
F6	0.9907 ± 0.006109	36.66 ± 0.5099	0.09 ±0.012	70.4 ±0.547
F7	1.3969± 0.02945	40 ± 0.3605	0.07 ±0.016	62 ±1.4142
F8	1.6175± 0.02475	46.66 ± 0.4582	0.09 ±0.015	63.8 ±0.4472
F9	1.6003± 0.00526	50 ± 0.4062	0.07 ±0.017	65.8 ±1.0954

Table 5. Evaluation Parameters of Formulation.

Characteristic	Folding Endurance Mean ± SD	Surface pH Mean ± SD	Disintegration Time(sec) Mean ± SD	Uniformity of Drug Content (%) Mean ± SD
F1	219 ± 3.6742	6.24 ±0.0223	18.3 ±1.218	92.13 ±0.01430
F2	207 ± 5.6347	6.21 ±0.0132	20.6±0.583	92.03 ±0.01575
F3	192 ± 4.4158	7.36 ±0.0304	21.3±1.528	93.51 ±0.01266
F4	183 ± 3.807	6.43 ±0.0312	13.6±1.157	93.79 ±0.02482
F5	180 ± 3.162	7.14 ±0.0390	16±1.000	94.76 ±0.02509
F6	182 ± 2.3048	6.08 ±0.0494	14.6±1.157	96.75 ±0.05802
F7	166 ± 2.7386	6.65 ±0.0331	11±1.732	95.76±0.04109
F8	176 ± 5.1961	6.91 ±0.00452	13±1.000	97.91 ±0.01407
F9	170 ± 1.87	6.51 ±0.025	11.3±0.578	98.7 ±0.05217

Table 6. *In-vitro* drug release study of all formulations.

Time (Min)	Cumulative drug release (%) ±SD								
	F1	F2	F3	F4	F5	F6	F7	F8	F9
1	66.85 **±0.3716**	69.82 **±0.2206**	70.55 **±0.3900**	75.16 **±0.2206**	82.13 **±0.4350**	84.97 **±0.4964**	86.97 **±0.4052**	80.57 **±0.4135**	94.73 **±0.2930**
2	69.71 **±0.3028**	74.13 **±0.2109**	72.92 **±0.3100**	81.47 **±0.2594**	88.07 **±0.4350**	88.32 **±0.8056**	89.53 **±0.3176**	82.92 **±0.2523**	96.44 **±0.2206**
3	72.63 **±0.6061**	77.29 **±0.3336**	80.50 **±0.5876**	87.90 **±0.3750**	90.99 **±0.750**	90.27 **±0.1951**	90.39 **±0.2636**	85.96 **±0.4053**	97.24 **±0.1609**
4	73.60 **±0.1343**	78.51 **±0.1682**	81.60 **±0.1403**	89.30 **±0.6158**	93.55 **±0.2206**	90.52 **±0.2260**	91.06 **±0.2902**	88.82 **±0.7269**	97.31 **±0.1473**
5	75.01 **±0.1609**	79.67 **±0.7054**	83.67 **±0.6075**	91.01 **±0.4135**	93.92 **±0.2411**	93.01 **±0.3327**	92.35 **±0.2854**	91.07 **±0.3763**	98.26 **±0.5202**

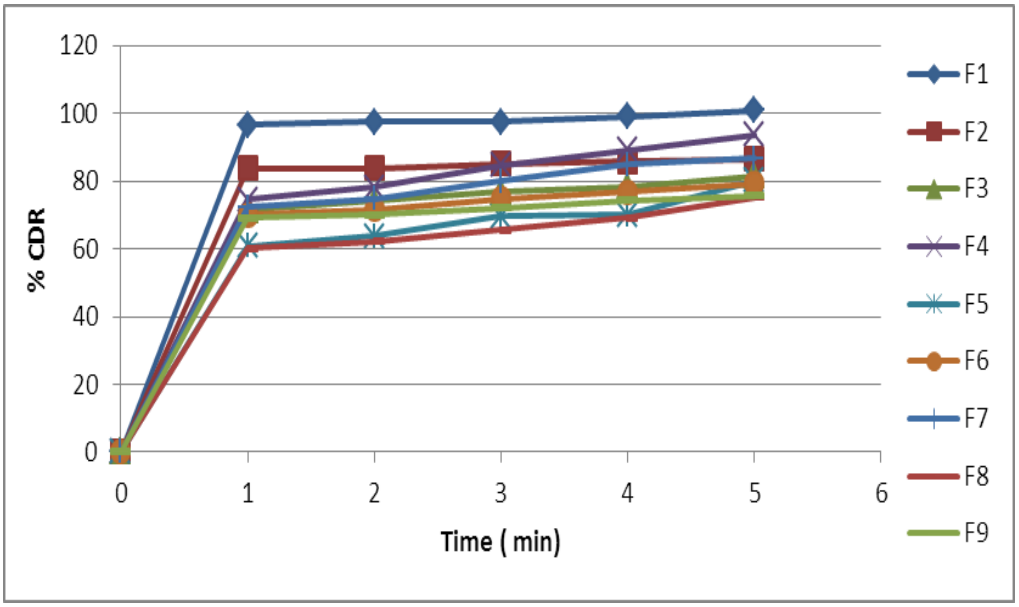

Fig 1: Comparative Evaluation of *in-vitro* drug release study of formulation.

Table 7. ANOVA for % drug release (Y1).

Source	Degree of Freedom	F value	P-value	Inference
Model	2	11.09	0.0097	Significant
A-GR Gum	1	19.34	0.1436	
B- PVP K-30	1	2.83	< 0.0046	

The perturbation plot

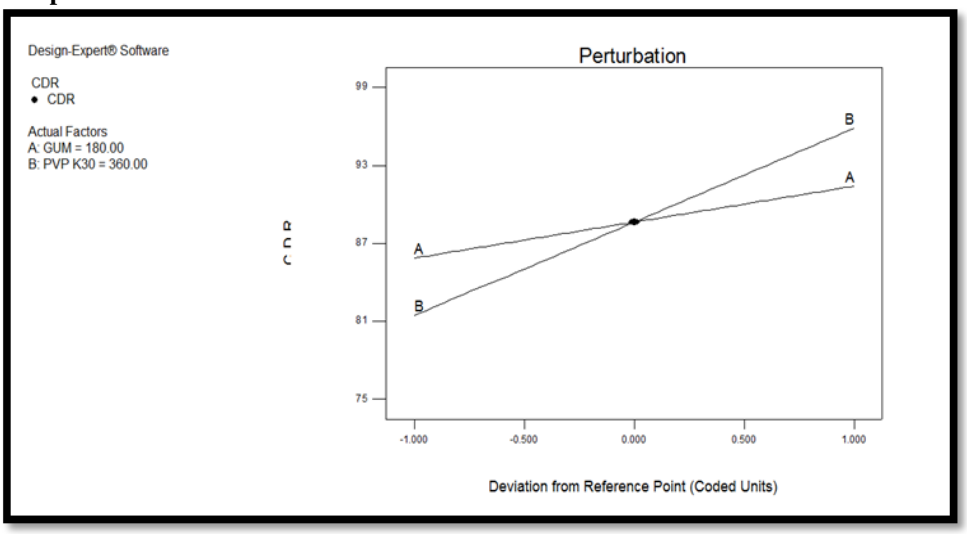

Fig. 2: Perturbation plot.

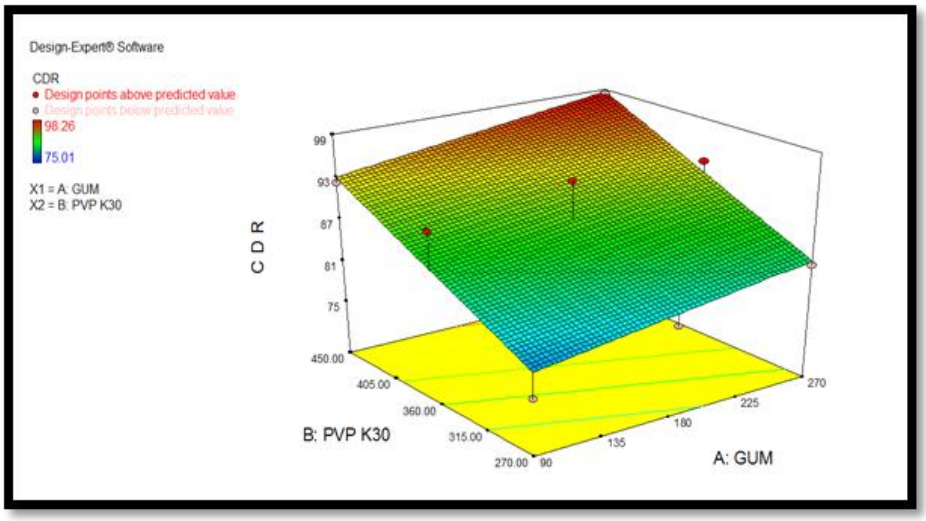

Fig.3: Surface Response plot showing effect of polyvinyl pyrrolidone K-30 and GR Gum on release.

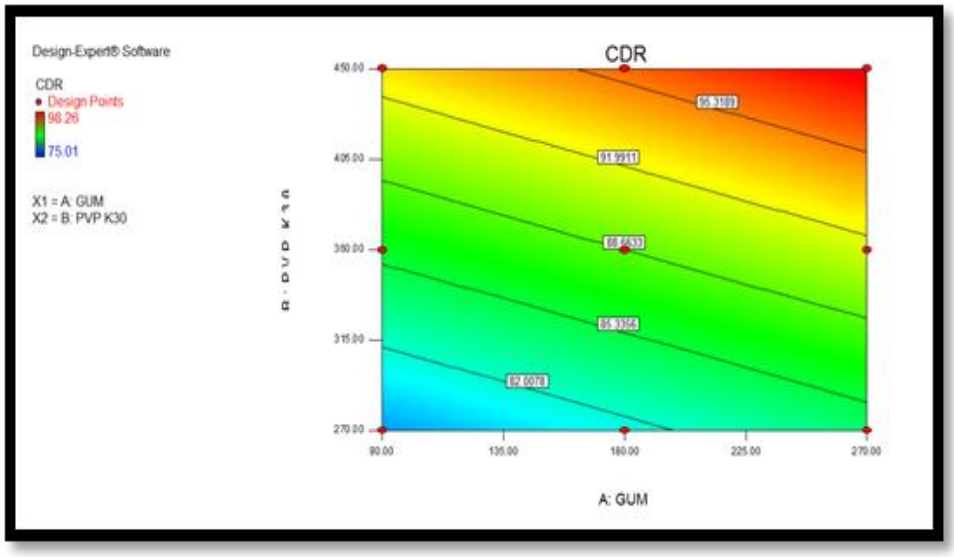

Fig 4: The contour plot showing effect of polyvinyl pyrrolidone K-30 and GR Gum on release.

Design summary and Response summary shown in Table. 9 and Table. 10 respectively.

Table 8. Design Summary.

Factor	Name	Units	Type	Mini	Max	-1 Actual	+1Actual	Mean	Std. Dev.
A	GR Gum conc.mg	mg	Numeric	90	270	90	270	180	0.82
B	PVP conc. mg	mg	Numeric	270	450	270	450	360	0.82

Table 9. Response Summary.

Response	Name	Units	Obs	Analysis	Mini	Max	Mean	Std. Dev.	Ratio	Trans	Model
Y1	% CDR	%	9	Polynomial	75.01	98.26	86.63	8.49959	1.34082	None	Linear

STABILITY STUDY

Formulation F9 at 40^{o}C temperature is found to be stable up to six months. There is no significant change in drug content, visual appearance i.e. change in color and disintegration time. All wafers stored at elevated temperature showed slight change in pH, other parameters were found to be unchanged. This change in pH was due to presence of PVP which was alkaline in nature, but it did not affect stability of drug within the wafer.

CONCLUSION

Wafers were prepared with different wafer formers such as GR Gum and PVA, in combination with PVP as a superdisintegrant by solvent casting method. The nine preliminary trial batches arranged/prepared by using the 3^2 factorial design lead to the final optimized concentration of the factors. The drug loaded wafers of all batches were evaluated for weight variation and thickness uniformity, tensile strength and percent elongation showed satisfactory result. The wafers were exhibited optimal folding endurance without any batch variation. Surface pH was determined for all formulations show acceptable pH range 6-7.4. This study also reflexed the influence of concentration of PVP in the formulation. The increased in proportion of PVP greater the pH of the formulation, as PVP was more alkaline to PVA. Disintegration time study showed that as increased in concentration of superdisintegrant leads to decrease in time to disintegrate. The formulations determine fairly uniform drug content ranging from 92.03 to 98.7% with minimum of batch variability. Formulation F9 showed the highest drug release upto 98.26%. This may be due to the concentration of polymers as well as superdisintegrant and showed suitability of drug for administered as a oral dissolving dosage form. The stability studies carried out over accelerated stability conditions for six months. Optimized sample was evaluated mainly for its physical characteristics at the predetermined intervals like appearance (colour changes), pH and drug content and disintegration time. The results favour the stability and compatibility of the formulation within stability studies. Finally it was concluded that the drug release from the fast dissolving oral wafer was increased by using the increased concentration of superdisintegrant and GR Gum thus assisting in faster disintegration in the oral cavity. As the drug was having low solubility, fast disintegration may lead to more drug availability for dissolution, resulting in faster absorption in systemic circulation. Increased systemic availability of drug will lead to quick onset of action, which was prerequisite for arthritis patients.

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