Research Article

Design, Development and Characterization of Mouth Dissolving Tablet of Antivirals

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Abstract:

Objective: The main objective of this research work was to design, develop and characterization of mouth dissolving tablet of antivirals.

Method: In this study, mouth dissolving tablet was prepared by direct compression method by using natural karaya gum, and synthetic sodium starch glycolate as Superdisintegrants in various concentrations. The designed tablets were subjected to various assessments parameters like hardness test, friability test, in *vitro* disintegration time, wetting time, *in vitro* drug release, and drug content.

Result: All the ready formulations were subjected to various assessments parameters, and the findings obtain within the approved limit. A1-A9 containing karaya gum, and sodium starch glycolate in various concentrations demonstrate the minimum disintegration time. Among all these formulations A9 shows disintegration time upto 15±1s due to the high concentration of superdisintegrants. *In vitro* drug release was tested in 0.1N HCl at a time interval of 0,2,4,6,8,10,12,14,16 min. The A9 shows drug release 99.4%. Accelerated stability study of optimized formulation (A9) up to 3 mo showed there was no change in disintegration time and percentage drug release.

Conclusion: The results found in the present research work clearly showed a positivepossible of mouth dissolving tablets containing a specific ratio of karaya gum and sodium starch glycolate as superdisintegrants.

Key Words: Acyclovir, Karaya gum, sodium starch glycolate, MDT.

Introduction:

Despite the brilliant inventions in drug delivery, the oral route remains the able route for administration of therapeutic agents because of accurate dosage, low cost of therapy, self-medi- cation, non-disturbing method, easy to administration leading to the high level of patient's compliance. Tablet and capsule are the most important dosage forms. But one important drawback of such dosage forms is dysphagia or difficulty in swallowing. To solve the above- mentioned problem, pharmaceutical technologies have put in their best efforts to develop a mouth dissolving drug delivery. Mouth dissolving tablets, the recent advancements in technology have resulted in the development of viable dosage alternative popularly as orally disintegrating tablets. The oral route is a useful method of administration when a rapid start action is desired[(1)]. MDT will rapidly disintegrate in the mouth without the need of water. MDT formulation provides sufficient strength, quick disintegration / dissolution in the mouth without water, rapid dissolution and absorption of the drug, which will produce the quick onset of action. Pre-gastric absorption of MDT can result in improved bioavailability and consequences of reduced dose. In addition, MDT is applicable when local action is desirable, such as oral ulcers, cold sores, and teething. The Acyclovir is used as the model drug. Acyclovir [9-(2-hydroxyethoxylmethyl) guanine], a synthetic purine nucleoside analog derived from guanine, is the most widely used antiviral agent. It is effective in the treatment of herpes simplex virus (HSV), mainly HSV-1 and HSV-2 and Varicella zoster virus (VZV). Acyclovir is poorly water-soluble and has poor bio- availability (15-30%), the peak plasma concentration occurs after 1-2 h when taking in orally. Protein binding is reported to range from 9-30 % elimination half-life($t_{1/2}$) range from 2-4 h. Molecular formula C8H11N5O3 Molecular weight 225.20g/mol water solubility at 37^0C is 2.5mg/ml. pka's 2.27and 9.25. Frequency of administration of acyclovir is high, being 200mg five times a day up to 400mg five times a day depending upon the type of infection [(2-5)]**.** Natural karaya gum and synthetic sodium starch glycolate superdisintegrant are used in the present study. The innovative part of this study is the natural and synthetic superdisintegrants are used to offers various advantages like safety, biodegradability, easy compressibility, low cost, etc[(6-10)]. Direct compression technique is used in the f ormulation of mouth dissolving tablets[(2)]**.** A $3^{(2)}$ full factorial design applied for the optimization of the mouth dissolving tablets of Acyclovir.

The aim of the present research work was to design, develop and optimize mouth dissolving tablets of Acyclovir

employing a combination of natural and synthetic superdisintegrant. Thus, the objective of the work was to design, develop and optimize the mouth dissolving tablet of Acyclovir, having adequate mechanical strength, rapid disintegration, and fast action.

Material And Methods:

Material:

Acyclovir was obtained as a gift sample from Torrent Pharmaceutical Ltd. Sodium starch glycolate, Karaya gum, Colloidal silicon dioxide, Sodium saccharine, Magnesium stearate, Mannitol and Avicel PH102 was obtained from Research lab, Fine chem. Indus- tries, Mumbai.

Preparation of Mouth Dissolving Tablets:

The tablets were prepared by direct compression method**.** The composition of different formulations of acyclovir mouth dissolving tablets is shown in Table 1**.** The uniformity in the particle size of each ingredient was achieved by passing through sieve no.16. All ingredients were accurately weighed and mixed using mortar and pestle and then added to Acyclovir and lubricating agent magnesium stearate. Finally, mixed blend was compressed by using eight stations rotary tablet presses (MINIPRESS)[2].

Drug Excipients compatibility studies:

Differential scanning calorimetry: DSC was used to characterize the thermal properties of Acyclovir, physical mixtures of acyclovir with natural superdisintegrant karaya gum, and synthetic superdisintegrant sodium starch glycolate compressed Mouth dissolving tablet. The DSC thermograms were recorded using Star e software (METTLER TOLEDO). The samples were heated in a crimped aluminum pan with a pierced lid at a scanning rate of 10° C/min in an atmosphere of nitrogen flow 50 ml/ min using a range of 40 to 350°C.

FTIR spectroscopy: FTIR spectra were recorded for Acyclovir, physical mixture, and compressed tablet using IR−spectrophotometer (Shimadzu). The samples were prepared in KBr dish and scanned over 400 to 4000 $cm^{(-1)}$**.**

Experimental design: To study the effect of variables, batches were prepared using $3^{(2)}$ factorial designs. The amount of karaya gum and sodium starch glycolate were selected as two independent variables and three levels are studied. Investigational variables and their coded levels with actual values are given in Table 1. High, mediumand low levels of each factor were coded +1,0and -1 respectively.

Table 1: Factorial Variables and levels

Variables and levels	Low (-1)	Medium (0)	High (+1)
Concentration of Karaya gum	5	10	15
Concentration of Sodium starch glycolate	10	15	20

Table 2: Formulation of tablet of Acyclovir MDT's

Ingredient (mg/tablet)	A1	A2	A3	A4	A5	A6	A7	A8	A9
Acyclovir	200	200	200	200	200	200	200	200	200
Karaya Gum	5	10	15	5	10	15	5	10	15
Sodium starch glycolate	10	10	10	15	15	15	20	20	20
Colloidal silicon dioxide	2	2	2	2	2	2	2	2	2
Sodium saccharine	1	1	1	1	1	1	1	1	1
Mg. stearate	2	2	2	2	2	2	2	2	2
Mannitol	5	5	5	5	5	5	5	5	5

Total weight of each tablet: 250mg.

Evaluation

Precompression parameters

Bulk density: Bulk density (g/ml) was determined by three-tap method in the graduated cylinder[6].

Bulk Density = Total mass of powder / Bulk volume of powder

(BD = M/ VB

Tapped density: It is the ratio of the total weight of powder to the tapped volume of powder. The volume was measured by tapping the powder for 100 times in Tap Density Apparatus for 4 minutes. The tapped volume was noted. It is expressed in g/ml[6].

Tapped Density = Total mass of powder / Tapped volume of powder

(TD) = M / Vt

Compressibility index /Carr's index:

It indicates powder flow properties[6]. It is expressed in percentage and is given,

$$(CI) = TD - BD / TD \times 100$$

Hausnerratio: Hausner ratio of the drug was measured using the following formula[6].

$$\text{Hausner ratio} = BD / TD$$

Angle of repose: Angle of repose was measured by the fixed funnel method. The friction strength in a loose powder can be measured by the angle of repose (θ). It is indicative of the flow parameters of the powder. It is defined as a maximum angle possible between the surface of the stack of powder and the horizontal plane[6].

$$(\theta) = \tan^{-1} h/r$$

Where, θ is the angle of repose, h is the height in cm and r is the radius in cm.

Post-compression parameters:

Hardness: The hardness of prepared formulation was measured by using Digital hardness tester[6].

Thickness: Thickness was measured using Vernier caliper tester. For each batch, three tablets were tested immediately after compression[6].

Weight variation: Twenty tablets randomly were selected and individually were weighed from the lot. Then, the individual weight was compared with that of average weight and the amount of weight variation was determined[6].

Friability: The friability of tablets was measured using USP type Roche friabilator. Preweighed tablets were placed in plastic chambered friabilator attached to motor revolving at a speed of 25 rpm for 4 min. The tablets were then dedusted, reweighed, and percent weight loss was calculated using the formula,[6]

$$\% \text{ Friability} = (wb - wa) / wb \times 100$$

Where, Wb-before weight of the tablet, Wa- after weight of the tablet.

Drug content uniformity: Twenty tablets were weighed and powdered a quantity of powder equivalent to 100mg of acyclovir was accurately weighed and extracted with a 100ml volume of distilled water. Then 10min sonication, after sonication its filter out and each extract was suitably diluted and analyzed spectrometrically at 254 nm[3].

Wetting time: A petridish containing 6 ml of Distilled water was used. A tissue paper folded twice was kept in the dish and a tablet was positioned on it. A small quantity of amaranth red color was placed on the upper surface of the tablet. The time required for the upper surface of the tablet to become red was noted as the wetting time of the tablet[6].

***Invitro* Disintegration Time:** Tablet was placed in a beaker containing 20ml of distilled water at 37±0.5^{0}C. The time for the disintegration of the tablet was measured in triplicate[11].

***In vitro* Dissolution studies**: The *In-vitro* dissolution rate study Acyclovir mouth dissolving tablets were performed using 8 stations dissolution test apparatus (Electrolab TDT-08) fitted with paddles (50rpm) at 37± 0.5^{0}C, using 0.1N HCl (900ml) as a dissolution media. At the predetermined time intervals, 5 ml samples were withdrawn, filtered through a 0.45µ membrane filter, diluted and assayed at 254 nm using a UV/ Visible Double beam spectrophotometer. Cumulative percentage of drug release was calculated using the standard absorbance from the calibration curve[3].

Stability studies: The stability study of the optimized mouth dissolving tablet of Acyclovir (A9) was carried out according to ICH guidelines at 40^{0}C ±2^{0}C and 75^{0}C ±5^{0}C for 3 mo by storing the samples in the stability chamber[2].

Results:

Drug and excipients compatibility: DSC study:

From the DSC thermogram of pure acyclovir and optimized formulation (A9), it was showed there is no interaction between the drug and polymer (Fig.1).

Fig.1: DSC thermogram of pure Acyclovir

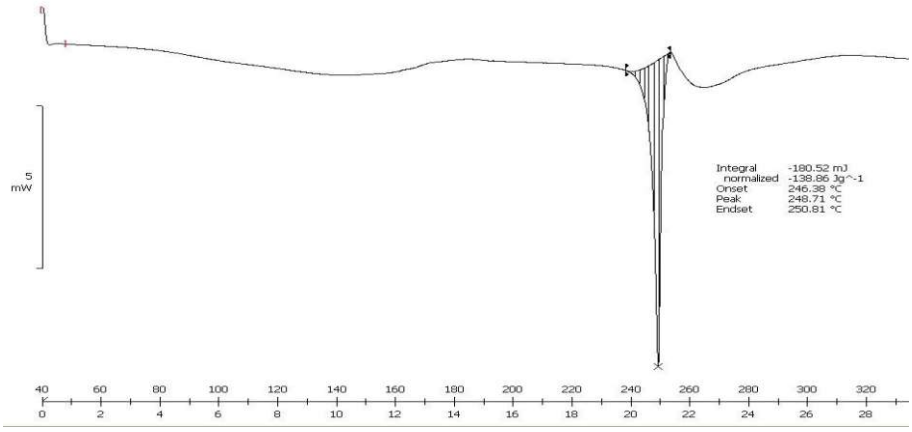


Fig.2: DSC thermogram of Optimized formulation (A9)

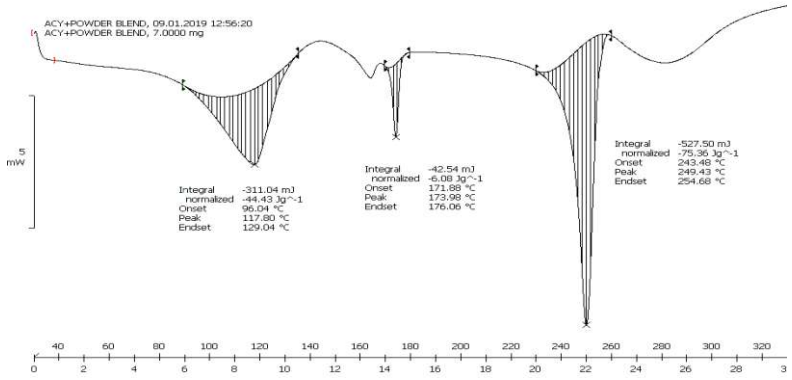


Fig.3: FTIR of Pure Acyclovir

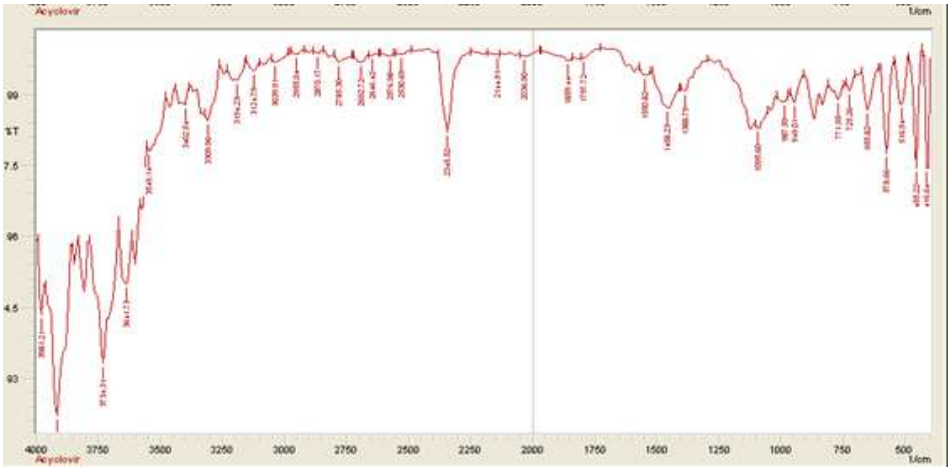
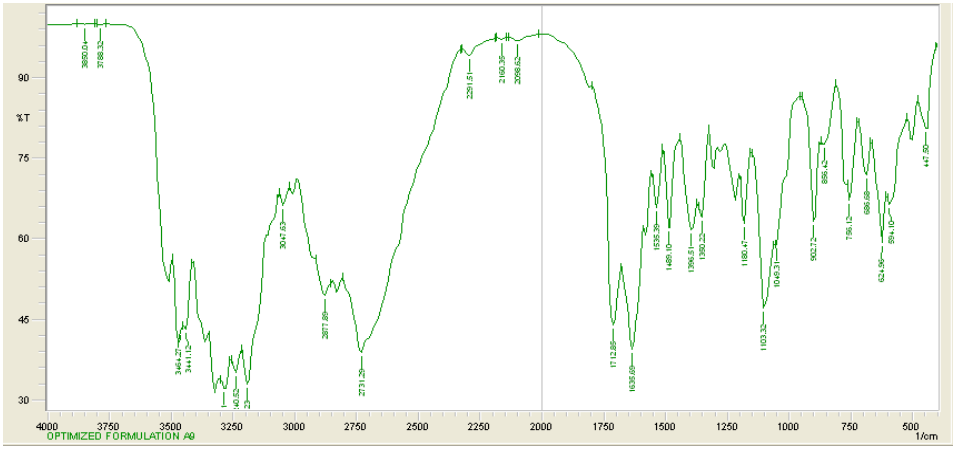


Fig.4: FTIR of optimized formulation (A9)



FTIR study:

The IR spectra of Acyclovir, polymers, andthe physical mixture are shown in Fig.3,4. The IR absorption bands observed in the IR spectrum of the drug and polymers resemble that of founding in physical mixture proves the compatibility of the drug with polymers.

Precompression evaluation parameters of powder:

Bulk density: Bulk density was found in the range of 0.40±0.04 to 0.53±0.04 g/ml.

Tapped density: Tapped density was found to be in the range of 0.45±0.02 to 0.61±0.0.4 g/ml.

Percentage Carr's index: Carr's index was found to be in the range of 13.04 ±0.06% to19.23±0.04 %.

Hausner ratio: Hausner ratio was found to be in the range of 1.09±0.12 to 1.2±0.13.

Angle of Repose: Angle of Repose was found to be in the range of 21.26±0.13^0 to 28.66±0.08^0.

Table 3: Precompression evaluation parameters

Formulation	*Bulk Density (g/ml)	*Tapped Density (g/ml)	*Carr's index (%)	*Hausner ratio	*Angle of repose (^{0})
A1	0.45 ±0.05	0.52±0.02	13.46±0.02	1.15±0.12	27.47±0.06
A2	0.43±0.03	0.52±0.04	15.68±0.05	1.18±0.11	27.92±0.14
A3	0.53±0.04	0.61±0.04	13.11±0.04	1.15±0.12	24.75±0.11
A4	0.44±0.03	0.51±0.04	13.72±0.04	1.15±0.10	24.96±0.13
A5	0.40±0.04	0.52±0.05	16.66±0.06	1.2±0.13	24.75±0.09
A6	0.43±0.02	0.48±0.05	15.68±0.05	1.18±0.11	26.36±0.10
A7	0.41±0.06	0.51±0.04	13.12±0.03	1.09±0.12	28.66±0.08
A8	0.42±0.02	0.45±0.02	19.23±0.04	1.23±0.10	28.34±0.11
A9	0.40±0.04	0.46±0.02	13.04±0.06	1.15±0.11	21.26±0.13

*All values are mean± SD of three determinations. SD: Standard deviation

Post-compression evaluation of mouth dissolving tablets of Acyclovir

Hardness: Hardness of the tablets varied between 3.12±0.11 kg/cm2to 3.72±0.16 kg/cm2 indicating good binding, and satisfactory strength of tablets to withstand stresses during transportation, and also may offer good dissolution property.

% Friability: The % friability was found in the range of 0.15% to 0.78%.

Weight variation: Ranges from 248±1to250±2 mg which passes the standard limits as per IP.

Thickness: The thickness of the tablets was found to be uniform, between 3.9±0.15mm to 4.2±0.32mm for all factorial batches.

Drug content: Drug content found in the MDT resembling that of literature value. Range of drug content is 95.04% to 102.72%. Therefore uniformity of content was maintained in all formulations. Drug content of all formula- tions is listed in table 4.

Wetting time:

It is the time required for complete wetting of tablet. The wetting time was found in the range of 45±2.0 to 58±0.5 s.

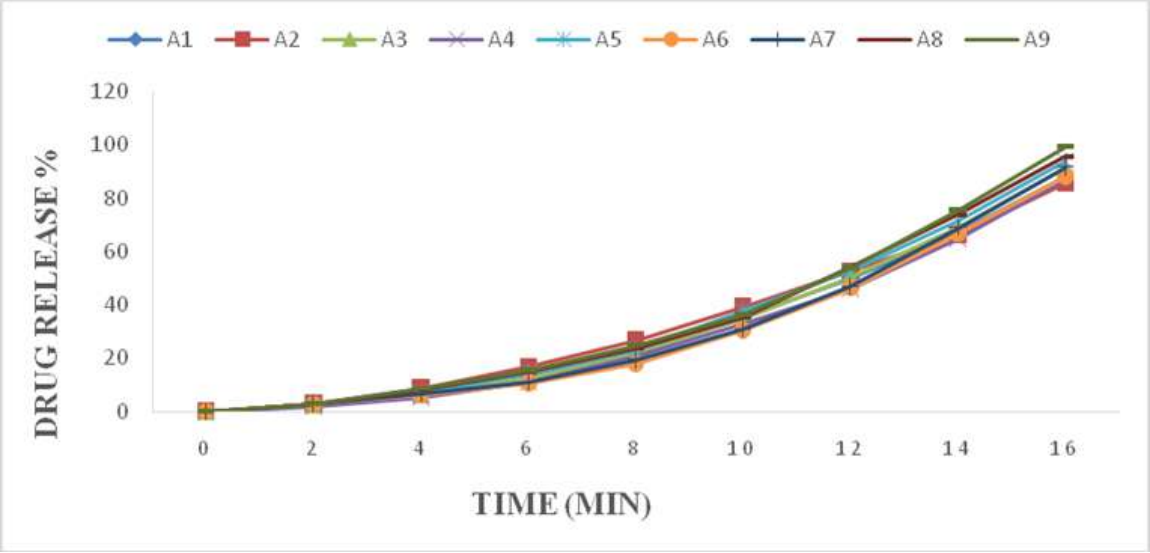
Disintegration time:

It is the time required for complete disintegration of the tablet. The disintegration time was found in the range of 15±1 to 48±1 s.

% Cumulative drug release:

% cumulative drug release was found in the range of 85.73 % to 99.4%.

Fig.5: % Cumulative release pattern



% cumulative drug release of the different formulations is shown in Fig.5. In this formulations as the level of natural karaya gum and synthetic sodium starch glycolate, superdisintegrant is increased the drug release will also increase. The release of the drug *in vitro* was determined by estimating the dissolution profile, USP(type II) paddle apparatus was used-acceptable to rotate at 50 rpm, 0.1 N HCL (900 ml) was used as a dissolution medium.

Table 4: Post compression parameters

Code	*Disintegration Time (s)	*Wetting time (s)	%Drug release
A1	48±1	58±0.5	87.91
A2	46 ± 2	54±0.5	85.73
A3	43± 2	51±0.5	91.65
A4	38±1	49±0.5	87.05
A5	32±2	50±0.1	93.93
A6	28±3	50±1.5	88.15
A7	37±1	48±1.0	91.56
A8	30±2	49±2.0	95.77
A9	15±1	45± 2.0	99.4

*All values are mean± SD of three determinations. SD: Standard deviation

Table 5: Post compression parameters

Code	*Hardness (kg/cm2)	*Thickness (mm)	Friability (%)	*Weight Variation (mg)	Drug Content (%)
A1	3.4 ±0.12	4.0±0.20	0.78	248±1	95.04%
A2	3.32±0.1	4.1±0.35	0.23	249±1	97.07%
A3	3.42±0.14	4.1±0.30	0.47	250±2	96.12%
A4	3.72±0.16	4.0±0.20	0.31	249±1	96.45%
A5	3.26±0.1	3.9±0.15	0.31	249±2	96.28%
A6	3.12±0.11	4.2±0.32	0.23	250±1	95.93%
A7	3.59±0.16	3.9±0.15	0.39	250±1	102.72%
A8	3.60±0.12	4.2±0.20	0.31	248±2	98.78%
A9	3.28±0.06	4.0±0.15	0.15	249±1	100.26%

*All values are mean± SD of three determinations. SD: Standard deviation

Stability study

Results of the stability studies showed that there is no change in the physical parameters of the formulation. Drug content, disintegration time and wetting time of the formulation were also found to be the same as that before stability testing. Stability data are shown in Table 6.

Table 6: Stability studies as per ICH guidelines

Temperature Condition	Color	Odor	Disintegration Time (s)	Wetting Time (s)	% Drug content (%)
Initial one month					
40°C/75 % RH	White	Odorless	15	46	97.07%
Two month					
40°C/75% RH	White	Odorless	18	49	95.93%
Three Months					
40°C/75 % RH	White	odorless	17	47	96.28%

Optimization

The purpose of the 3^2factorial design was to conduct the comprehensive study of the effect of process parameters like natural karaya gum (X1) and synthetic sodium starch glycolate (X2) and their interactions using a suitable statistical tool (MINITAB 17.0) by applying one way ANOVA at 0.05 levels. Analysis of variance for disintegration time study and friability was performed. The coefficients X1 (Karaya gum and X2 (sodium starch glycolate) showed a significant effect (0.05) on selected responses.

The response surface plots for dependent variables disintegration time and friability were generated and the effect of independent variables, X1,and X2 on responses was studied (Fig. 6).The effect of formulation variables on disintegration time can be described by model equation 1,

Disintegrational Time = 61.33 - 2.82 x 1 + 0.333 x 2 + 0.1733x12 - 0.1650x1x2

---- (equation 1)

The negative sign for coefficient X1 and X2 indicated that as the concentration of natural and synthetic superdisintegrant increased disintegration time decreased indicating a good correlation between independent and dependent variables. The term with ($P<0.01$) was considered significant.

The parameter friability can be described by the model equation,

Disintegrational Time = 1.165 - 0.1067X1 - 0.01733X2 + 0.00430X12

---- (equation 2)

The negative sign for coefficients X1 and X2 suggests increases in the concentration of superdisintegrants decreased friability. The effect of independent variables on friability was significant ($P<0.01$) and indicates a good correlation (Fig.7).

Fig.7: Surface plot of %friability

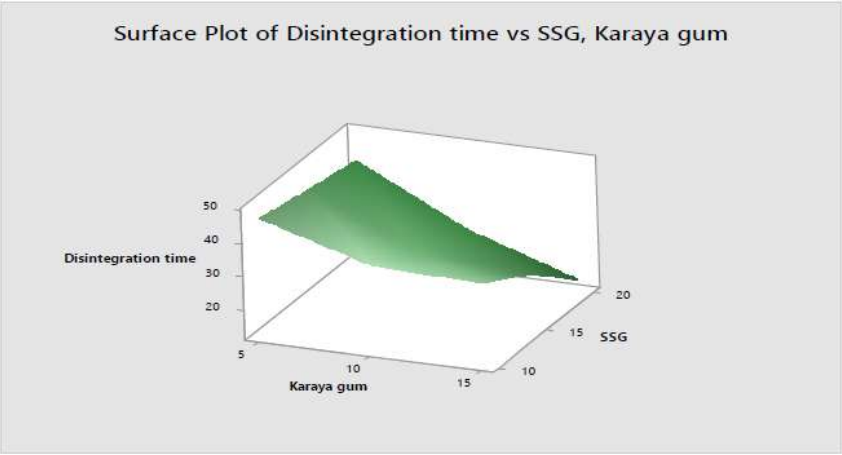
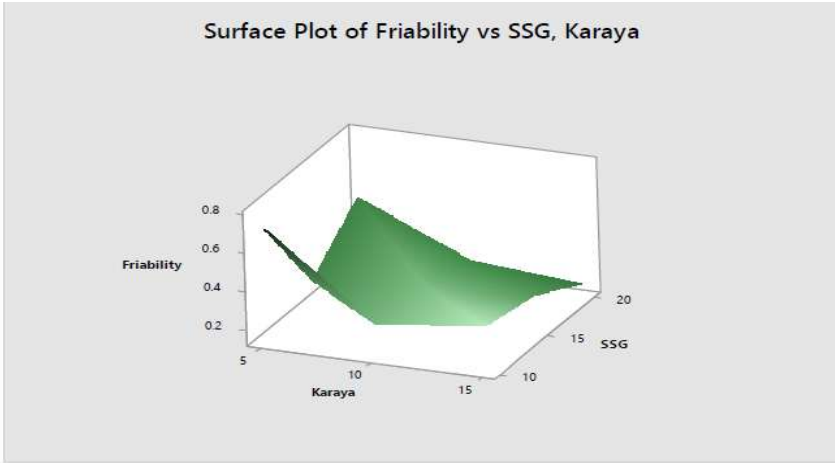


Fig.7: Surface plot of %friability



Discussion:

DSC of pure Acyclovir drug showed a sharp endothermic peak at 248.71 ^{0}C which was near to the melting point range (250-252^{0}C). The nature of the peak showed the purity of the Acyclovir drug.

DSC of optimized formulation (A9) showed that there was no interaction between drug and excipients. The FTIR of pure drug Acyclovir and an optimized batch (A9) showed all peak ranges are uniform. NH stretch (primary amine) of pure drug Acyclovir obtained at 3402.54 cm^{-1} and that of an optimized batch (A9) showed at 3302.24 cm^{-1}. C-N (aromatic) of the pure drug showed a peak at 1388.79 cm^{-1} and that of optimized formulation (A9) showed at 1304.78 cm^{-1}. O-H stretching of the pure drug showed a peak at 3549.14 cm^{-1} and for optimized formulation (A9) at 3660.17 cm^{-1}. C=O stretching of the pure drug acyclovir showed a peak at 1797.72 cm^{-1} and for optimized formulation (A9) at 1643.41 cm^{-1}. DSC and FTIR study showed that drug and excipients are compatible with each other. From the FTIR and DSC studies, it is clear that there is no interaction between drug and excipients as the principle peaks of the pure drug are not affected in IR spectrum of the drug along with polymers and no shifting of the melting point of the drug in the optimized formulation of drug.

Tablet blend was investigated for bulk density, tapped density, compressibility index, Hausner's ratio, and angle of repose. All parameters for batch (A1) to (A9) were within the limit and showed good flow property. Hardness and thickness of all formulation were found to be uniform and it ensures good handling characteristics and good mechanical strength of all the batches. The percentage friability of all formulation was less than 1% indicating good mechanical characteristics. The optimized formulation A9 showed less % friability as compared to other formulation due to a higher concentration of natural and synthetic superdisintegrant (Karaya gum and Sodium starch glycolate) used in combination which was essential for making less friable tablets. All the prepared tablets of acyclovir had been evaluated for weight variation. The weight of tablets was found to be uniform and was within acceptable the Pharmacopoeial limits. The percent drug content of the entire tablet was found in the range which was within limits which indicates the uniform mixing. Wetting time decreased from increasing the karaya gum and sodium starch glycolate concentration superdisintegrants. Lower wetting time gives faster disintegration in the A9 formulation batch as compared to other batches. Disintegration time is the significant parameter for the determination of an optimum mouth dissolving tablet formulation. This study, showed that disintegration time is decreased because of tablets containing a high concentration of karaya gum and sodium starch glycolate used in combination which absorbs water and swells causing the rupture of the tablets. Tablet prepared by the wet granulation technique showed disintegration time at 45 sec[(5)]. So, as per the above result, direct compression technique was better than the wet granulation method.The results obtained from the dissolution study were summarized in table 4 and fig.5. In the present study, the dissolution of acyclovir was enhanced by using the natural and synthetic superdisintegrant agent in different concentration in combination. Super- disintegrants can absorb the water, swells and rupture the tablets, thereby enhances the dissolution and bioavailability. A9 formulation made from karaya gum and sodium starch glycolate (15:20 mg) concentration showed the highest percentage drug release. It was clear from the obtained results that the concentration of superdisintegrant directly proportional to the dissolution rate. The A9 formulation showed a percentage drug release of 99.4 % within 16 min. The stability study showed that there were no major changes made on tablets. The three- level and two factors employed in the experimental design are indicated in table 1. The disintegration time and percentage friability indicate that the dependent variables strongly depend on independent variables. The negative sign for the coefficient of X1X2 in equation 1 indicates that as the concentration of karaya gum and sodium starch glycolate increases disintegration time decreases. In equation 2 the negative sign for X1 and X2 indicates that increasing concentration of superdisintegrant friability decreases. The effect of independent variables on disintegration time and friability is significant and indicates a good correlation. The response surface plots were presented to show the effects of X1 and X2 on disintegration time and friability (fig. 6, 7).

Conclusion:

The present studies are aimed at successful design, development, and characterization of the mouth dissolving tablet of Acyclovir. Among the prepared batches of tablets based on performance with respect to friability, hardness, drug content, disintegration time, wetting time and *in vitro* drug release studies, A9 delivers the best results as compared to other formulations. Thus, drug release from the mouth dissolving tablet was increased by using the increased concentration of superdisintegrants (natural and synthetic) in combination, assisting in faster disintegration in the oral cavity. As the drug having fast disintegration may lead to more drug availability for dissolution, resulting in faster absorption and possibly bioavailability leads to the quick onset of action in the systemic circulation.

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Authors Contribution:

Mr. Jitendra Shinde and Miss. Ashwini Kumbharkar contributed to design and implementation of the research to analysis of results and to writing of manuscript.

Source of Support: Nil

Conflict of Interest: Nil

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