

Evaluation of Dikamali as a Tablet Binder in Zidovudine Tablets

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Abstract

The aim of the present study is to evaluate the gum, Dikamali, as a tablet binder employing zidovudine as a model drug. Zidovudine tablets were prepared by wet granulation technique using Dikamali as a tablet binder. The Dikamali was used in wet form and dry form. Granules were evaluated for pre-compression parameters: tapped density, bulk density, compressibility index, hausner ratio, and angle of repose. All the parameters were found to be within the acceptable limits. The tablets were evaluated for hardness, friability, weight variation, disintegration, content uniformity, and dissolution.

For the formulations F1-F3D; F1-F3W; F4-F7 (see Table 1) the parameters of friability, disintegration time, and hardness were measured and their values range from 0.57-0.73% (w/w), 0.83-0.97% (w/w), 0.69-0.99% (w/w); 12-13 min, 10-12 min, 10-12 min; and 5-6.9 kg/cm², 4.5-5.1 kg/cm², 4.1-5.2 kg/cm²; respectively. The binding efficacy of Dikamali was compared with the standard binders, starch mucilage and polyvinyl pyrrolidone, using dissolution studies. The binders, Dikamali and starch, were compared at similar concentrations [2.5% (w/v), 5% (w/v), and 7.5% (w/v)], and the finalized formulation (F1D) was compared with a 10% (w/v) concentration of starch mucilage and a 10% (w/v) concentration of polyvinyl pyrrolidone (PVP). Dikamali [2.5% (w/v)] in dry form (i.e. F1D) showed the same percent drug release as that of the 10% (w/v) of starch mucilage and of polyvinyl pyrrolidone. In conclusion, Dikamali could well be used as a binding agent in the formulation of tablet dosage forms, and Dikamali is more effective in dry form than the wet form.

Keywords: Dikamali, zidovudine, binder, natural gum, tablet.

Introduction

Now-a-days, there is an increasing importance to natural polymers for their use especially as natural binders, emulsion stabilizers, suspending agents, thickeners [1], sustain-release polymers, disintegrants [2], and potential carriers in site specific delivery [3]. Natural gums are economical, easily available, and useful as tablet binders. The growing significance to natural polymers is due to their advantages, such as biodegradability, biocompatibility, non-toxicity, local availability, better patient tolerance, as well as public acceptance [4]. In addition, most of the gums are obtained from edible sources. Globally available natural polymers are from different origins including land plants (potato starch [5], gum ghatti, gum karaya, gum tragacanth [6], gum Dikamali) land animals (chitin and chitosan, chondroitin sulfate), marine plants and animals (agar, carrageenans, alginic acid), and microbials (xanthan gum, dextran, baker's yeast glycan) [7].

We chose to use Dikamali in this study. To the best of our knowledge, no significant work has been reported on Dikamali as a tablet binder. Dikamali is one such natural gum of the shrub *Gardenia gummiifera* belonging to the family *Rubiaceae* [8, 9]. It is a transparent greenish yellow color with a sharp pungent taste and peculiar odor [10]. It is an oleogum resin, containing mostly

polysaccharides, flavonoids, alkaloids, and proteins in small quantities. Commercial samples of Dikamali contain resins (89.9%), volatile oils (0.1%), and plant impurities (10%). Dikamali is commonly known by many names: pindava in Sanskrit; nadi-Hingu in Hindi; manchi bikki and tella manga in Telugu; kamarri in Gujarati; kambilippicin in Tamil; Dikamali in Bengal and Marati; and cittu-bikke and dikkemalli in Kannada [8].

Dikamali is soluble in different solvents like water, HCl (0.1N), NaOH solutions, and phosphate buffer at pH 7.4. [11]. Medicinal properties of Dikamali include anti-spasmodic, expectorant, carminative, diaphoretic, and anthelmintic property [12]. Physical and chemical properties of Dikamali include a melting point at 45-50°C, an acid value of 87.1, an iodine value of 80.8; and a saponification value of 172.3 [13]. It shows turbid precipitation with acetone, alcohol, and ether. Others have reported that the structure of Dikamali contains six new cycloartane triterpenes (i.e. Dikamaliartanes A-F), along with a known flavonoid, using NMR spectroscopy. All six cycloartanes are characterized by an open A-ring with a free COOH group at 3-C. In four of them, the C-atoms, C (23)-C (27), form a 4-methylfuran-2-yl moiety [14]. Preliminary phytochemical investigation of Dikamali demonstrates that Dikamali shows positive results for Molisch's test, Fehling's test, Benedict's test, the tannic acid test, a test for flavonoids, and a test for gums and a negative result for Barford's test. From these data



one can conclude that Dikamali is a composite of flavonoids and carbohydrates, specifically polysaccharides.

Zidovudine (AZT) is the drug of choice for AIDS treatment [15]. Zidovudine is a nucleoside reverse transcriptase inhibitor (NRTI), which shows action against Human Immunodeficiency Virus Type 1 (HIV-1) by converting into its active form, zidovudine triphosphate [16]. Zidovudine's half life is 4 hours and shows protein binding of 30-38%. It is a white or brownish powder, which is soluble in ethanol (67 mg/ml), water (25 mg/ml), 0.1N HCl (28 mg/ml), and phosphate buffer at pH 6.8 (20.1 mg/ml.) [17]. Rapid and nearly complete absorption of zidovudine from the gastrointestinal tract follows oral administration; however, because of first-pass metabolism, systemic bioavailability of zidovudine is approximately 65% (i.e., 52-75%). After intravenous dosing, about 29% of the dose, that was excreted in the urine, was unchanged, and about 45% of the dose was excreted as GZDV (glucuronide form of zidovudine) [18].

This manuscript mainly discusses the use of Dikamali as a simple binder as well as its future scope to use it as a sustain-release polymer. Dikamali has been established as a tablet binder by performing dissolution studies. Dikamali was used as a solution and dry powder, and the dry powder showed a greater potential as a tablet binder.

Materials and Methods

Materials

Zidovudine was received as a gift sample from Hetero Drugs Private Limited (Hyderabad, India). Dikamali was received as a gift sample from Girijen Co-operative Corporation (Vishakhapatnam, India). All the other chemicals used for study were purchased from Finar Chemicals.

Methods

Tablet Preparation

Different zidovudine formulations containing Dikamali as a binder were prepared by wet granulation technique. Formulations (F1 to F7) were developed as shown in Table 1. Zidovudine and other excipients were weighed accurately and mixed with distilled water to prepare samples of uniform mass. Each prepared mass was passed through #16 mesh, and the resultant granules were dried in a hot air oven at 60°C for 20 min. The dried granules were passed through #22 mesh and then treated with magnesium stearate and talc. Dried granules were subjected to suitable compression using tablet compression machine (Rimek). In the wet granulation technique, binder was used in dry form as well as wet form. In dry form Dikamali was used as a powder, and in wet form Dikamali was used as a solution by dissolving in distilled water [19, 20].

Table 1: Formulation series:

Gives an idea about how the different formulations were designed.

Formulation (F)	Zidovudine (mg)	Dikamali (mg)	Starch paste (mg)	Starch (mg)	Lactose (mg)	Magnesium stearate (mg)	Total (mg)
F1 (D)	300	12.5	-	50	132.5	5	500
F1 (W)	300	12.5	-	50	132.5	5	500
F2 (D)	300	25	-	50	120	5	500
F2 (W)	300	25	-	50	120	5	500
F3 (D)	300	37.5	-	50	107.5	5	500
F3 (W)	300	37.5	-	50	107.5	5	500
F4	300	-	12.5	50	132.5	5	500
F5	300	-	25	50	120	5	500
F6	300	-	37.5	50	107.5	5	500
F7	300	-	50	50	95	5	500

F1, F2, and F3 are the formulations containing Dikamali as a binder. 'D' denotes the Dikamali in dry form; 'W' denotes the Dikamali in wet form. F4-F7 are the formulations containing starch paste as a binder

Physical characterization of granules

FTIR studies were carried out to identify any possible chemical interaction between zidovudine and Dikamali. IR spectrums of Zidovudine, Dikamali, and their physical mixture were recorded using KBr pellets. The spectra were scanned over a wavenumber range of 4200 to 500 cm^{-1} [21]. The granules were also tested for angle of repose [22], bulk density, tapped density, compressibility index, and Hausner's ratio according to standard procedures [23].

Evaluation of tablets

The prepared matrix tablets were evaluated for weight variation, hardness, friability, disintegration, and content uniformity using reported procedures. Weight variation was evaluated on 20 tablets using an electronic balance, and the test was performed according to a commonly used method. Friability was determined by taking 10 tablets in a Roche friabilator for 4 min at 25 rpm. Tablet hardness was determined for 6 tablets using a Monsanto hardness tester. The drug content of the manufactured tablets of each batch was determined in triplicate. For each batch 20 tablets were taken, weighed, and finely powdered. An accurately weighed quantity of powder was taken and analyzed after making appropriate dilutions with water [24, 25].

In vitro drug release study

The in vitro release of zidovudine from formulated tablets was carried out for 60 minutes in phosphate buffer at pH 7.4. The studies were performed in a USP Dissolution Apparatus II (Paddle type) at 37 ± 0.5 C and 50 rpm speed. Samples were taken at 5, 10, 15, 30, 45, and 60 minutes intervals, diluted to suitable concentration, and analyzed for zidovudine content at 267 nm by using UV-visible spectrophotometer [26].

Results and Discussion

In the present study different concentrations of binders: Dikamali (D) and starch (S) [2.5% w/v D, 5% w/v D, 7.5% w/v D, 2.5% w/v S,



5% w/v S, 7.5% w/v S, and 10% w/v S] were used. Tablets of zidovudine were prepared using Dikamali as a binder both in wet form and dry form using wet granulation technique, shown in Table 1. A total of ten different formulations were prepared, in which 6 formulations have Dikamali (F1 to F3 D, W) and 4 formulations have starch paste (F4 to F7) as a binder. UV-Visible spectra showed characteristic λ_{max} of zidovudine at 257nm. FTIR spectra of zidovudine (Fig. 1), Dikamali (Fig. 2), and their physical mixture (Figure. 3), were taken. The comparison of all the three spectra was shown in Figure. 4. All the characteristic peaks of pure drug, such as, C-N amine stretching ($1030-1250\text{cm}^{-1}$), N-H stretching ($3200-3500\text{ cm}^{-1}$), C=O stretching ($1600-1700\text{cm}^{-1}$), and O-H stretching ($3100-3400\text{cm}^{-1}$) were observed in the spectrum of drug zidovudine and Dikamali mixture indicates that there was no interaction between the drug and polymer.

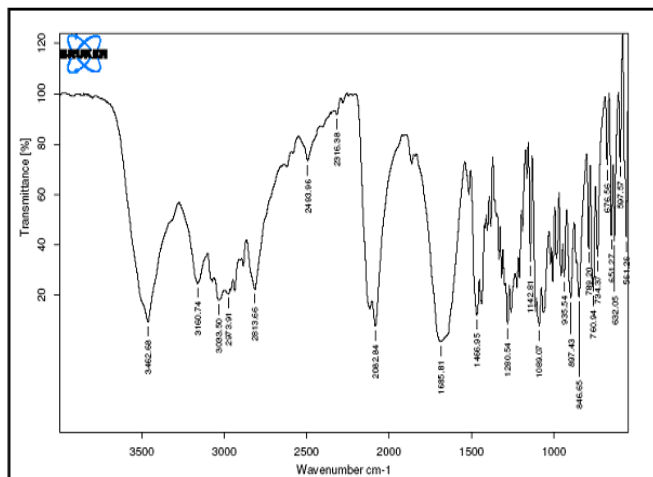


Figure. 1: FTIR Spectra of Zidovudine showing different stretching vibrations of pure drug

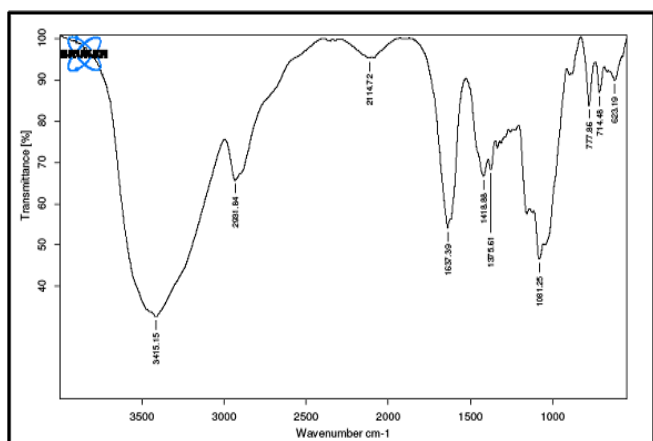
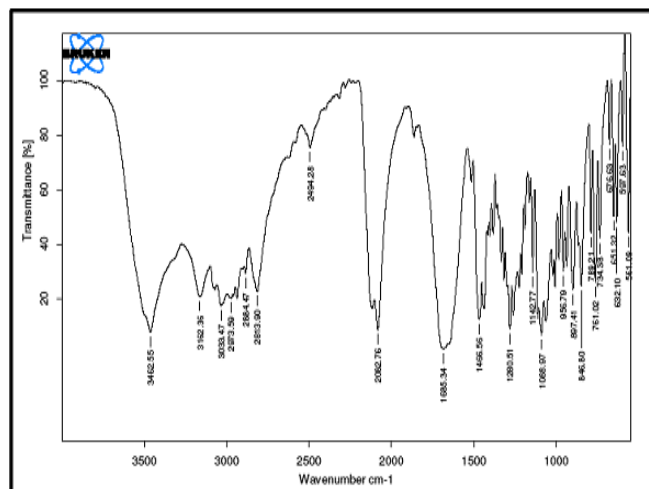
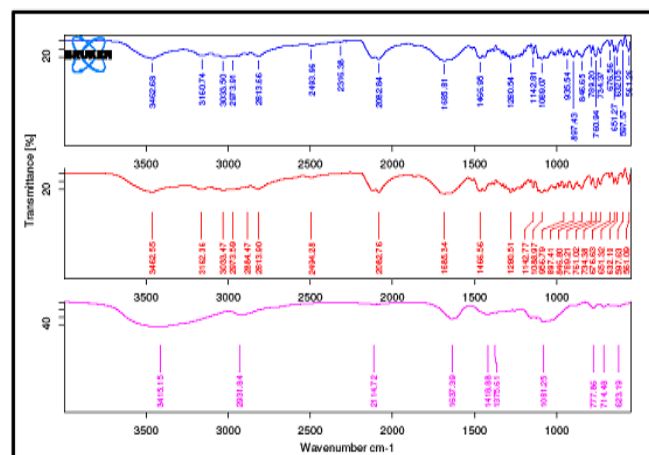


Figure. 2: FTIR Spectra of Dikamali showing absorption bands of different functional groups as generally shown by natural gums.



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Figure. 3: FTIR Spectra of Zidovudine-Dikamali Mixture



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Figure. 4: Comparison FTIR Spectra of Zidovudine (Blue), Zidovudine+Dikamali (Red), Dikamali

The prepared granules were tested for flow properties: angle of repose, bulk density, tapped density, compressibility index, and Hausner's ratio. Even though all the formulations showed results within limits, the formulations containing dry Dikamali (F1 to F3 D) showed accurate results compared to formulations containing Dikamali solution (F1 to F3 W). The results were shown in Table 1 and Table 3. The compressed tablets were evaluated for hardness, friability, weight variation, disintegration, and content uniformity. Tablets with dry Dikamali (F1 to F3 D) were harder, more friable, and displayed less disintegration time than tablets containing Dikamali solution (F1 to F3 W). The results were shown in Table 2 and Table 4.



Table 2: Characterization of Granules

The results of different evaluation parameters done on granules those were prepared using binder in dry form.

Formulation	Angle of Repose (\square)	Bulk density (gm.cm^{-3})	Tapped density (gm.cm^{-3})	Compressibility index (%)	Hausner's ratio
F1D	18 \pm 0.5	0.44 \pm 0.02	0.51 \pm 0.098	13.7 \pm 0.5	1.15 \pm 0.07
F2D	19 \pm 0.6	0.48 \pm 0.03	0.57 \pm 0.046	15.7 \pm 0.41	1.18 \pm 0.02
F3D	20 \pm 0.2	0.47 \pm 0.06	0.56 \pm 0.073	16.07 \pm 0.78	1.2 \pm 0.043
F4	22 \pm 0.8	0.48 \pm 0.02	0.59 \pm 0.047	18.64 \pm 0.32	0.62 \pm 0.05
F5	19 \pm 0.4	0.45 \pm 0.04	0.55 \pm 0.063	18.18 \pm 0.027	0.82 \pm 0.063
F6	20 \pm 0.5	0.44 \pm 0.01	0.53 \pm 0.067	16.9 \pm 0.54	0.43 \pm 0.039
F7	23 \pm 0.8	0.44 \pm 0.07	0.50 \pm 0.034	12.9 \pm 0.2	1.2 \pm 0.02

Values \pm S.D.; n=3

Table 3: Evaluation of Tablets

Different evaluation parameters done on tablets those were prepared using binder in dry form.

Formulation	Hardness (Kg.cm^{-2})	Friability (% w/w)	Wt variation (mg)	Disintegration (min)	Content uniformity (%w/w)
F1D	5 \pm 0.42	0.57 \pm 0.12	500.15 \pm 1.11	12 \pm 0.9	99 \pm 0.18
F2D	6.2 \pm 0.57	0.63 \pm 0.09	499.18 \pm 2.54	13 \pm 1.0	98 \pm 0.92
F3D	6.9 \pm 0.38	0.73 \pm 0.05	505.15 \pm 1.11	13 \pm 0.5	103 \pm 0.45
F4	4.1 \pm 0.74	0.69 \pm 0.14	501.02 \pm 4.34	10 \pm 1.2	92 \pm 0.72
F5	5 \pm 0.43	0.81 \pm 0.07	492.9 \pm 3.52	10 \pm 0.8	101 \pm 0.21
F6	5.5 \pm 0.84	0.99 \pm 0.11	500.15 \pm 1.50	12 \pm 1.3	93 \pm 0.83
F7	5.2 \pm 0.54	0.59 \pm 0.55	500.22 \pm 1.12	12 \pm 1.2	99 \pm 0.45

Values \pm S.D.; n=3

Table 4: Characterization of Granules

Different evaluation parameters done on granules those were prepared using binder in wet form.

Formulation	Angle of Repose (\square)	Bulk density (gm.cm^{-3})	Tapped density (gm.cm^{-3})	Compressibility index (%)	Hausner's ratio
F1W	22 \pm 0.6	0.45 \pm 0.02	0.52 \pm 0.098	15.7 \pm 0.5	1.20 \pm 0.07
F2W	26 \pm 0.6	0.47 \pm 0.01	0.57 \pm 0.046	16.7 \pm 0.91	1.17 \pm 0.06
F3W	22 \pm 0.8	0.48 \pm 0.07	0.58 \pm 0.074	17.07 \pm 0.48	1.18 \pm 0.051
F4	22 \pm 0.8	0.48 \pm 0.02	0.59 \pm 0.047	18.64 \pm 0.32	0.62 \pm 0.05
F5	19 \pm 0.4	0.45 \pm 0.04	0.55 \pm 0.063	18.18 \pm 0.027	0.82 \pm 0.063
F6	20 \pm 0.5	0.44 \pm 0.01	0.53 \pm 0.067	16.9 \pm 0.54	0.43 \pm 0.039
F7	23 \pm 0.8	0.44 \pm 0.07	0.50 \pm 0.034	12.9 \pm 0.2	1.2 \pm 0.02

Values \pm S.D.; n=3

Table 5: Evaluation of Tablets

Different evaluation parameters done on tablets those were prepared using binder in wet form.

Formulation	Hardness (Kg.cm^{-2})	Friability (% w/w)	Wt variation (mg)	Disintegration (min)	Content uniformity (%w/w)
F1W	4.5 \pm 0.72	0.90 \pm 0.12	492.15 \pm 1.11	10 \pm 0.8	98 \pm 0.18
F2W	5.0 \pm 0.75	0.83 \pm 0.08	509.18 \pm 2.54	11 \pm 1.0	97 \pm 0.92
F3W	5.1 \pm 0.38	0.97 \pm 0.05	505.15 \pm 1.11	12 \pm 0.9	103 \pm 0.54
F4	4.1 \pm 0.74	0.69 \pm 0.14	501.02 \pm 4.34	10 \pm 1.2	92 \pm 0.72
F5	5 \pm 0.43	0.81 \pm 0.07	492.9 \pm 3.52	10 \pm 0.8	101 \pm 0.21
F6	5.5 \pm 0.84	0.99 \pm 0.11	500.15 \pm 1.50	12 \pm 1.3	93 \pm 0.83
F7	5.2 \pm 0.54	0.59 \pm 0.55	500.22 \pm 1.12	12 \pm 1.2	99 \pm 0.45

Values \pm S.D.; n=3

Dissolution studies were performed on ten different formulations. Comparing equal concentrations of Dikamali and starch as binders, Dikamali formulations showed the better results compared to starch (Figure. 5 and Figure.7). Overall, the formulations with 2.5% w/v Dikamali (F1D and F1W) were finalized because at the lowest possible concentration they showed 95% and 98% drug release in 60 minutes with correlation coefficients of 0.983 and 0.932 for F1D and F1W, respectively. The final formulations were compared with two standard binders: starch and polyvinyl pyrrolidone at their standard concentration of 10% w/v by using the dissolution technique (Figure.6 and Figure.8). It was observed that the F1D formulation showed exactly the same result as that of formulations containing standard binders; whereas, F1W displayed deviation in percent drug release. The reason why F1D showed improved results compared to F1W is the Dikamali, in the F1W formulation, was initially dissolved in water, and Dikamali solution was used in the F1W formulation as a binder. So, in the wet form the pore size of Dikamali polymer was increased and passage channels got widened which allowed faster release of drug with a poor regression coefficient. However, in the F1D formulation there was no previous contact of Dikamali with water until the last step of preparation. So, F1D showed constant drug release similar to standard binders with a good regression coefficient, although, it took more time to release 99% of drug than F1W. A lower concentration of Dikamali than standard binders could be used to achieve the same level of binding. Drug release from the F2D and F3D was very slow because the high concentration of binder hindered the drug release by providing a greater hardness and compactness to the formulation. This property of binder indicates that the Dikamali should be investigated as a sustain release polymer. Finally, the formulation containing 2.5% w/v Dikamali in dry form (F1D) was proven as the best formulation.



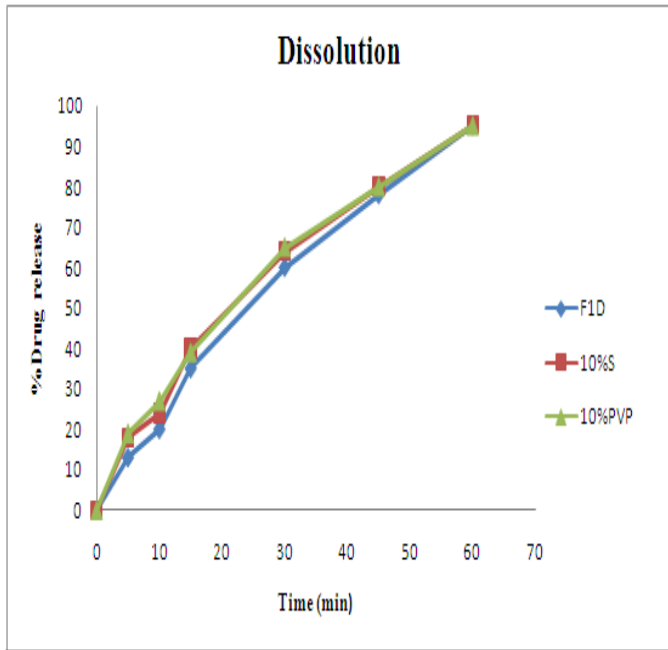


Figure. 5: Drug release pattern of seven different formulations prepared using the Dikamali and starch mucilage in dry form.

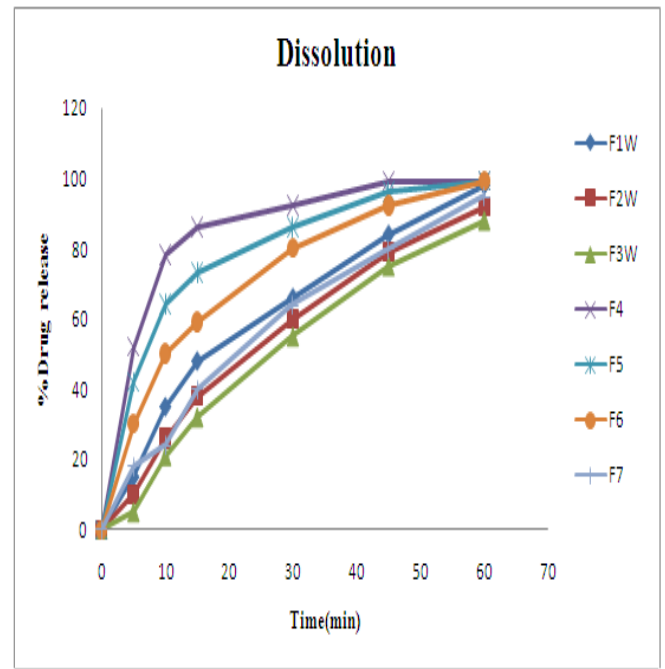


Figure. 7: Drug release pattern of seven different formulations prepared using the gum Dikamali and starch mucilage in wet form.

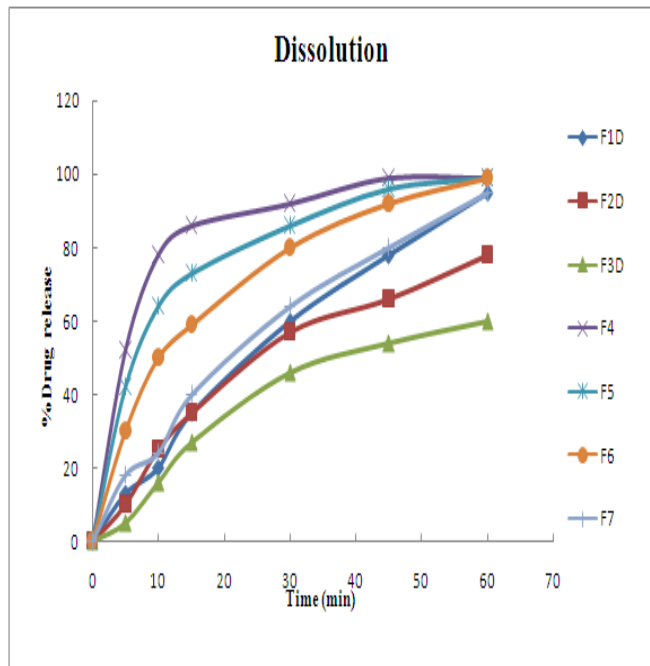


Figure.6: Comparison of F1 D (optimized formulation) drug release pattern with Standard binders: starch mucilage and PVP.

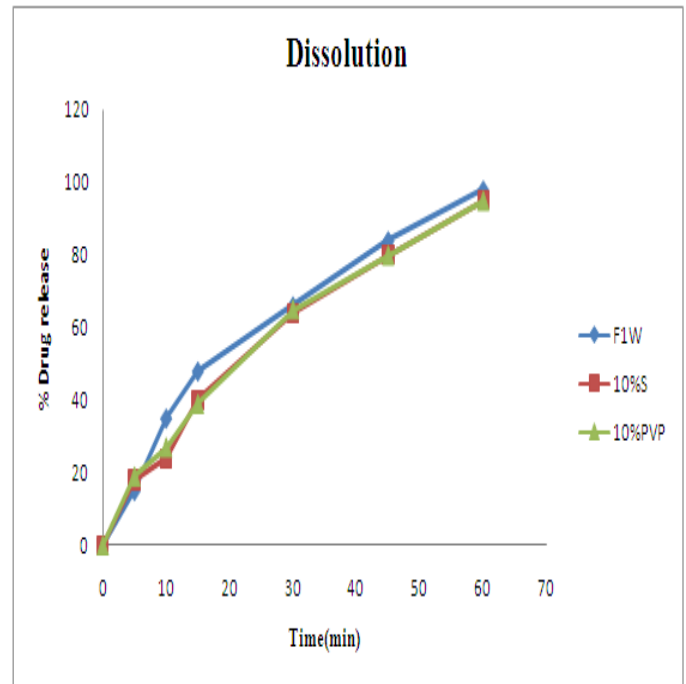


Figure.8: Comparison of F1W drug release pattern with Standard binders: starch mucilage and PVP.



Conclusion

The current study demonstrates that the tablets of zidovudine can be prepared by employing Dikamali alone as a binder. The evaluation of tablets has revealed that the binding efficacy of the tablets prepared using Dikamali at 2.5% concentration is comparable to the efficacy of the tablets prepared using 10% starch and 10% PVP as standard binders. Formulations containing Dikamali seem to produce more appropriate conventional tablets than other polymers at low concentrations. Dikamali be able to use as a binder in both dry and wet forms, but Dikamali in dry form is better than wet form. Therefore, Dikamali could be used well as a

binding agent in the formulation of tablet dosage forms. Future scope of this project is that Dikamali can be developed as a sustain release polymer at higher concentrations.

Acknowledgements

The authors are thankful to Centre for Pharmaceutical Sciences, Institute of Science and Technology, Jawaharlal Nehru Technological University, Andhra Pradesh, India for providing the necessary facilities and requirements for completing the research work.

References

- [1]. Oluremi BB, Bamiro OA, Idowu AO, Oduneye OA. Effect of compression pressure, preservative, and storage with potassium chloride on the microbiological quality of tablets formulated with *Terminalia randii* Gum (Combretaceae). *Pak J Pharm Sci.* 2012;25(4):773-776.
- [2]. Prajapati ST, Patel MV, Patel CN. Preparation and evaluation of sublingual tablets of zolmitriptan. *Int J Pharm Investig.* 2014;4(1):27-31.
- [3]. Suryawanshi SR, Thakare NP, More DP, Thombre NA. Bioavailability enhancement of ondansetron after nasal administration of *Caesalpinia pulcherrima*-based microspheres. *Drug Deliv.* 2013. [Epub ahead of print]
- [4]. Jacques Scholtz, Jaco Van der Colff, Jan Steenekamp, Nicole Stieger and Josias Hamman. More Good News About Polymeric Plant- and Algae-Derived Biomaterials in Drug Delivery Systems. *Curr Drug Targets.* 2014;15(5):486-501.
- [5]. Rahul V. Manek, Philip F. Builders, William M. Kolling, Martins Emeje, and Olobayo O. Kunle. Physicochemical and Binder properties of Starch obtained from *Cyperus esculentus*. *AAPS PharmSciTech.* Jun 2012; 13(2): 379–388.
- [6]. Gavligli HA, Michalak M, Meyer AS, Mikkelsen JD. Enzymatic depolymerization of gum tragacanth: bifidogenic potential of low molecular weight oligosaccharides. *J Agric Food Chem.* 2013;61(6):1272-1278.
- [7]. Girish K Jania, Dhiren P Shahb, Vipul D Prajapatia, Vineet C Jainb. Versatile excipients for pharmaceutical formulations. *Asian Journal of Pharmaceutical Sciences.* 2009; 4 (5): 309-323.
- [8]. Dr.K.S.Krishnan marg. Council of Scientific and Industrial Research. *Wealth of India.* New Delhi, India: CSIR Publishing house; 1956. 4. P.109-110.
- [9]. Lakavath S, Avula B, Wang YH, Rumalla CS, Gandhe S, Venkat rao AR. Differentiating the gum resins of two closely related Indian *Gardenia* species, *G. gummifera* and *G. lucida*, and establishing the source of Dikamali gum resin using high-performance thin-layer chromatography and ultra-performance liquid chromatography-UV/MS. *JAQAC Int, Pubmed.* 2012; 95(1): 67-73.
- [10]. C.P Khare (Ed.). *Encyclopedia of Indian Medicinal Plants.* New York, USA: Springer science + Business media; 2007.P. 230–231.
- [11]. Chopra RN. *Indigenous Drugs of India.* Kolkata, India: Bimal Kumar Dhur of academic publishers; 2006.P.137.
- [12]. Indian Council of Medical Research. *Phytochemical Reference Standards of selected indian medicinal plants.* New Delhi, India: Medicinal Plants unit publisher; 2010.P.143-151.
- [13]. Anandakumar A, muralidharan R, balasubramaniam M. Standardisation of Dikamali. *Ancient Science of Life;* 1984, 4(2): 106-109.
- [14]. Kunert O, Sreekanth G, Babu GS, Rao BV, Radhakishan M, Kumar BR. Cycloartane triterpenes from Dikamali, the gum resin of *Gardenia gummifera* and *Gardenia lucida*. *Chem biodivers (pubmed).*2009; 6(8):1185-1192.
- [15]. Santos JV, Pina ME, Marques MP, de carvalho LA. New sustained release of zidovudine matrix tablets - cytotoxicity toward Caco-2 cells. *Drug Dev Ind Pharm.* 2013 Aug; 39(8):1154-66.
- [16]. Santos JV, Batista de carvalho LA, Pina ME. The influence of the compression force on zidovudine release from matrix tablets. *AAPS Pharm Sci Tech.* 2010 Sep; 11(3):1442-1448.



- [17]. Martins EMEJE,* Olajide OLALEYE, Christiana ISIM. Oral Sustained Release Tablets of zidovudine Using Binary Blends of Natural and Synthetic Polymers. *Biol. Pharm. Bull.* 2010;33(9): 1561-1567.
- [18]. H.P Rang, M.M.Dale, J.M.Ritter. *Pharmacology*. Spain: Elsevier publications; 2007.p.684-685.
- [19]. Leon Lachman, Herbert A. Lieberman. *The Theory and practice of Industrial Pharmacy*. Bombay, India: Verghese publishing house; 1987.p.317-324.
- [20]. Bettini R, Colombo P, Massimo G, Catellani PL, Vitali T. Swelling and drug release in hydrogel matrices: Polymer viscosity and matrix porosity effects. *Eur J Pharm Sci.* 1994; 2: 213-219.
- [21]. Robert M. Silverstein, Francis X. Webster. *Infrared Spectrometry*. In: Robert M. Silverstein. editors. *Spectrometric Identification of Organic Compounds*. 6th Ed. John: Wiley and Sons. Inc. new York; 1997.p. 71 – 143.
- [22]. Cooper J, Gunn C. Powder flow and compaction. In: Carter SJ, editors. *Tutorial pharmacy*. New Delhi: CBS publisher and Distributors; 1986.p. 211-233.
- [23]. Aulton ME, Wells TI. *Pharmaceutics: The science of dosage form design*. London, England: Churchill Livingstone; 1998.p.647-649.
- [24]. Government of India, Ministry of Health and Family Welfare. *The Pharmacopoeia of India*. Delhi, India: Controller of Publication; 5th Ed., Vol.II;2007.p.41-42.
- [25]. Remington. *The Science and Practice of pharmacy*.19th Ed., Vol.I;1995.p.1669-1670
- [26]. Williams RL. (ed.) *The United States Pharmacopoeia*.29th ed. United States Pharmacopoeial convention Inc., Rockville; 2006.p.958-959.

