ejpmr, 2021,8(12), 458-463

SJIF Impact Factor 6.222

EUROPEAN JOURNAL OF PHARMACEUTICAL AND MEDICAL RESEARCH

www.ejpmr.com

Research Article

ISSN 2394-3211

EJPMR

STUDIES ON DESIGN AND DEVELOPMENT OF DISSOLVABLE ORAL DRUG DELIVERY SYSTEMS OF A POORLY WATER SOLUBLE NON-STEROIDAL ANTI-INFLAMMATORY DRUG

T. Sukanya*, S. Srivallika, D. Chandra Sekhar Naik, Aminul Islam Khan, Atif Hussain and Mehabub Hassan

Nimra College of Pharmacy, Jupudi, Ibrahimpatnam, Vijayawada, Andhra Pradesh.

***Corresponding Author: T. Sukanya**

Nimra College of Pharmacy, Jupudi, Ibrahimpatnam, Vijayawada, Andhra Pradesh.

Article Received on 12/10/2021 **Article Revised on 02/11/2021** **Article Accepted on 23/11/2021**

ABSTRACT

The main objective of the present research work is to develop fast dissolving tablets by employing 23 factorial designs with Starch xanthate. The physical and micrometric properties were performed to evaluate the synthesized starch xanthate. The fast-dissolving tablet of Diclofenac was prepared by employing starch xanthate as superdisintegrantin different proportions in each case by direct compression method using 23 factorial design. Starch xanthate exhibited good swelling in water. The study between Diclofenac and starch xanthate was shown the absence of interaction by Fourier transform infrared spectra (FTIR) and differential scanning calorimetry (DSC). The evaluation post parameters of fast dissolving tablets the optimized formulation is F2. The dissolution efficiency of Diclofenac was enhanced when starch xanthate was found to be a super disintegrants when combined with sodium starch glycolate, croscarmellose sodium and, hence it could be used in the formulation of fast dissolving tablets to provide immediate release of the contained drug within 10 min.

KEYWORDS: Fast dissolving, Superdisintegrant, Starch xanthate, Dissolution.

INTRODUCTION

Under the category of solid dosage forms, the fast dissolving tablets are containing indicated substances which disintegrate rapidly, usually within a few seconds when placed upon tonguerequiring additional water to facilitate swallowing. Fast dissolving tablets contribute immense advantages for the patients having dificulty in swallowing. It has been reported that dysphasia (dificulty in swallowing) is usual among all groups and more speciic with pediatric, geriatric population along with patients have nausea, retching, and motion sickness complications. Fast dissolving tablets overcome this problem and provide the advantages for pediatrics, geriatric, bedridden, disabled patients and also for who may have dificulty in swallowing tablets, capsules, and liquid orals. Fast dissolving tablets (FDT) will disintegrate rapidly in the mouth without the need of water. Fast dissolving tablet 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 FDT can result in improved bioavailability and as a consequence of reduced dose.[6] Various techniques can be used to formulate fast dissolving tablets. To achieve fast tablet disintegration, direct compression is one of the techniques used in the incorporation of super disintegrant or highly water-soluble excipients into the formulation. Direct compression is the ideal method for moisture and heat-liable medication and does not require the use of water or heat during the formulation procedure. The aim of the work was to formulate and characterize fast-dissolving tablets of Diclofenac by utilizing optimization techniques for rapid dissolution of drug and absorption employing a new super disintegrant i.e., starch xanthate.

The selection of several experimental and manufacturing steps for a given product and to quantitatively select a formulation, optimization techniques are used which provide both depth of understanding and an ability to explore and deine ranges for formulation and processing factors. It is at this point that optimization can become a useful tool to quantitative a formulation that has been qualitatively determined.

The current study focuses on an attempt to develop a systematic approach for optimising Diclofenac fast dissolving tablets using superdisintegrants such as starch xanthate, sodium starchglycolate, and croscarmellose sodium. To explore the main and interaction impacts of the three formulation variables, starch xanthate (A), sodium starch glycolate (B), and croscarmellose sodium (C) in each example, a 2^3 factorial design was used. The formula with less disintegration time and more dissolution eficiency 5 min and to permit arbitrary

selection oftablets with immediate release of drug within 10 min.

MATERIALS AND METHODS

Materials

Sodium hydroxide, Carbon disulphide, Mannitol was purchased from Finar chemicals Ltd, Ahmedabad. Potato starch, Sodium starch glycolate, Croscarmellose sodium wasobtained from Yarrow chem. products, Mumbai. Microcrystalline cellulose was bought from Qualigens ine chemicals, Mumbai. Talc and magnesium stearate was obtained from Molychem, Mumbai.

METHODS

Preparation of starch xanthate (a novel superdisintegrant)

Initially, 35.4 parts of potato starch were slurried in 225 ml distilled water and 8 parts of sodium hydroxide was dissolved in distilled water. Both are stirred continuously for 30 min. To this 5 parts of carbon, disulphide was added and stirred for 16 h at 25 °C. After 16h, it was filtered and washed with 75 ml of distilled water, 500 ml of acetone and 100 ml of ether. The product was kept in oven at 60 °C for 2 h. The product obtained was ground and sieved.

Characterization of starch xanthate

The starch xanthate prepared was evaluated for the following

Solubility Starch xanthate solubility was tested in various solvents like distilled water, aqueous buffers of pH 1,2,3,4,6 and organic solvents such as alcohol, dichloromethane, chloroform, acetone and petroleum ether.

pH The pH of 1% w/v slurry was measured by pH meter.

Melting point Melting point was determined by using melting point apparatus.

Viscosity Viscosity of 1% dispersion in water was measured using Ostwald viscometer

Swelling index Starch xanthate (200 mg) was added to 10 ml of water and light liquid paraffin taken in two different graduated test tubes and mixed. The dispersion in the tubes was allowed to stand for 12 h. The volumes of the sediment in the tubes were recorded.

The swelling index ( ) of the material was calculated as follows.

$$SI\% = \frac{\text{volume of sediment in water - volume of sediment in light liquid paraffine} \times 100}{\text{volume of sediment in light liquid paraffine}}$$

Test for gelling property Starch and starch xanthate prepared were evaluated for their gelling property by heating a 7% w/v dispersion of each in water at 100 °C for 30 min.

Particle size Particle size analysis was done by sieving using standard sieves.

Density Density (g/cc) was determined by liquid displacement method using benzene as liquid.

Bulk density Both loose bulk density (LBD) and tapped bulk density (TBD) were determined by transferring the accurate weighed amount of sample in 50 ml measuring cylinder, the granules without any agglomerates and measured the volume of packing and tapped 50 times on a plane surface and tapped volume of packing recorded and LBD and TBD calculated by following formula.

$$\text{LBD} = \frac{\text{Mass of powder}}{\text{Volume of packing}}$$

$$\text{TBD} = \frac{\text{Mass of powder}}{\text{Tapped volume of packing}}$$

Percentage compressibility index Percentage compressibility of the powder mix was determined by Carr's Compressibility Index calculated by the following formula.

$$\%\ \text{Carr's Index} = \frac{\text{TBD-LBD} \times 100}{\text{TBD}}$$

Where, TBD= Tapped bulk density; LBD= Loose bulk density.

Angle of repose The frictional forces in loose powder or granules can be measured by the angle of repose. This is the maximum angle possible between the surface of a mass of powder or granules and the horizontal plane. The angle of repose is calculated by applying the next equation; Where θ=angle of repose; h=height; r=radius

Fourier transform infrared (FTIR) spectroscopy FTIR spectra of starch xanthate were recorded on samples prepared in potassium bromide (KBr) disks using a BRUKER FT–IR, (Tokyo, Japan). The scanning range was 500 to 4000 cm-1. Samples were mixed with (KBr) to form disks by means of a hydrostatic press at 6-8 tons pressure [8]. X-Ray diffraction Diffraction pattern of starch xanthate was recorded with an x-ray diffractometer (analytical spectra's Pvt. Ltd., Singapore).

Preparation of Diclofenac fast dissolving tablets

The tablets were prepared by direct compression method employing 23 factorial design in which3 independent variables {superdisintegrants i.e., starch xanthate (A), sodium starch glycolate (B), croscarmellose sodium (C)} and 1 dependent variable (dissolution eficiency in 5 min) wereselected. The composition of the different formulation of Diclofenac fast dissolving tablets isshown in table no 1 in which the levels of super disintegrants were selected at 2 levels i.e., lowerand higher level concentrations. For starch xanthate (A), the lower level

i.e., 5% concentration and upper level i.e., 10% concentration. For sodium starch glycolate (B) and croscarmellose sodium(C), the lower level is zero concentration and higher level i.e., 5% concentration. For uniformity in particle size, each ingredient was passed through # 100 mesh sized screen beforemixing. Starch xanthate, sodium starch glycolate, croscarmellose sodium, mannitol and microcrystalline cellulose were accurately weighed and mixed using mortar and pestle, and theadded to Diclofenac. Finally, talc and magnesium stearate were added to the powder mixture. Finally, the mixed blend was compressed by using eight station rotator press KarnawathiMachineries Pvt, Ltd., Ahmedabad, India).

Formulae of Diclofenac sodium fast dissolving tablets.

Ingredints/mg	F1	F2	F3	F4	F5	F6	F7	F8
Diclofenac sodium	50	50	50	50	50	50	50	50
starch xanthate	---	12.5	---	12.5	--	12.5	--	12.5
Crospovidone	---	--	12.5	12.5	--	--	12.5	12.5
Croscarmellose sodium	---	--	--	--	12.5	12.5	12.5	12.5
Manitol	30	17.5	17.5	5	17.5	5	5	--
MCC	160	160	160	160	160	160	160	152.5
Talc	5	5	5	5	5	5	5	5
Mg sterate	5	5	5	5	5	5	5	5
Total	**250**	**250**	**250**	**250**	**250**	**250**	**250**	**250**

Friability

The friability of tablets was measured using a Roche fribilator. Tablets were rotated at 25 rpm for4 min or up to 100 revolutions. The tablets were then reweighed after removal of ines and thepercentage of weight loss was calculated.

Drug content uniformity

For content uniformity, ten tablets were weighed and powdered a quantity of powder equivalentto 10 mg of ibuprofen was extracted into 7.2 phosphate buffer and iltered. The ibuprofencontent was determined by measuring the absorbance spectrophotometrically at 221 nm afterappropriate dilution with 7.2 phosphate buffer. The drug content was calculated as an average ofthree determinations.

Wetting time

The wetting time of tablets was measured by placing ive circular tissue papers in a petri dish of10 cm in diameter. Ten ml of water containing a water-soluble dye (amaranth) was added to thepetri dish. A tablet was carefully placed on the tissue paper. The time required for water to reachthe upper surface of the tablet was noted as wetting time.

Water absorption ratio

A piece of tissue paper folded was kept in a small petri dish to which 6 ml of water was added. Atablet was kept on the tissue paper and allowed to completely wet. The wetted tablet was thenweighed. Water absorption ration R was determined using the following equation.

Evaluation of ibuprofen fast dissolving tablets

Hardness test

Hardness indicates the ability of a tablet to withstand mechanical shocks while handling. Thehardness of the tablet was determined using Monsanto hardness tester and expressed in kg/cm².[9]

Uniformity of weight

Weight variation test was done with 20 tablets. It is the individual variation of the tablet weighedfrom the average weight of 20 tablets.[10]

Where,

W1 = weight of tablet after water absorption.

W2 = weight of tablet before water absorption.

***In–vitro* disintegration time**

Disintegration time for FDTs was determined using USP disintegration apparatus 0.1 N HCl buffer.The volume of medium was 900 ml and the temperature was 37±0.2 °C. The time taken forcomplete disintegration of the tablet was measured.

***In–vitro* dissolution studies**

The *in vitro* dissolution rate study of ibuprofen fast dissolving tablets were performed using 8stage dissolution test apparatus (Electrolab TDT-08L) itted with paddles (50 rpm) at 37±0.5 °C,using 7.2 phosphate buffer (900 ml) as a dissolution media. At the predetermined time intervals,5 ml samples were withdrawn, iltered through a 0.45µ membrane ilter, diluted and assayed at221 nm using an Analytical technology T360 UV/Visible Double beam spectrophotometer.Cumulative percentage release was calculated using standard absorbance from the calibrationcurve. All the dissolution experiments were conducted in triplicate (n = 3).

RESULTS AND DISCUSSION

The prepared Starch xanthate was found to be fine, free flowing slightly amorphous powder. The physical and micromeritics properties of the Starch xanthateare summarized in table 1. It was insoluble in aqueous solvents and insoluble in organic solvents tested

(methanol, petroleum ether, dichloromethane, and chloroform) the pH of 3% aqueous dispersion. Starch xanthate exhibited good swelling in water. The swelling index was 50% all micrometric properties resulted good flow and compressibility needed for solid dosage from manufacturing. The density of Starch xanthate was found to be 0.514 g/cc. The angle of repose and compressibility index showed good flow properties of Starch xanthate.

The FTIR spectrum of potato starch and Starch xanthateis shown in fig:6.2 -6.4. The presence of peaks absorption at 2908.38 cm-1and 2927.26 cm-1 characteristic peaks of ester, so from FTIR studies it was concluded that Starch xanthate (ester) was formed when starch was allowed to react with formic acid. The X-ray diffraction pattern (fig: 6.2-6.4) of Starch xanthate showed no peaks, which indicates that the structure is slightly amorphous. The disappearance of pink colour in the ester test confirmed the presence of ester, i.e., Starch xanthate. As the Starch xanthate was slightly amorphous powder and it had got all the characteristic of superdisintegrants it was concluded.

physicochemical character of starch xanthate

Solubility	Insoluble in all aqueous and organic solvent tests
pH(1%w/v aqueous dispersion) 3.72	Melting point Charged at 300 Cº
Viscosity(1%w/v aqueous dispersion) 1.04cps	Swelling index 66.6%
Gelling properties	No gelling and the swollen particles of Starch separate from water. where as in thecase of starch, it was gelatinized and formed gel
Moisture absorption 4.1	Partial size 152µm (80/120) mesh
Density 0.514g/cc	Bluk density 0.562g/cc
Angle of response 13.03Cº	Compressibility 15.53%

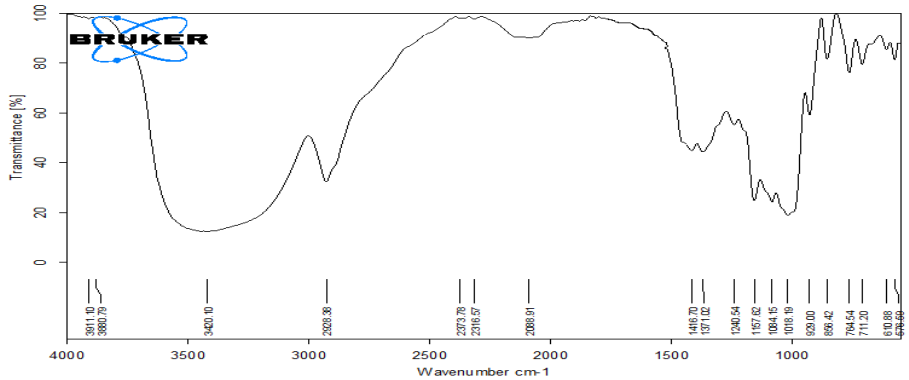

Fig No: 6.2 Fourier transform infrared spectra of potato starch.

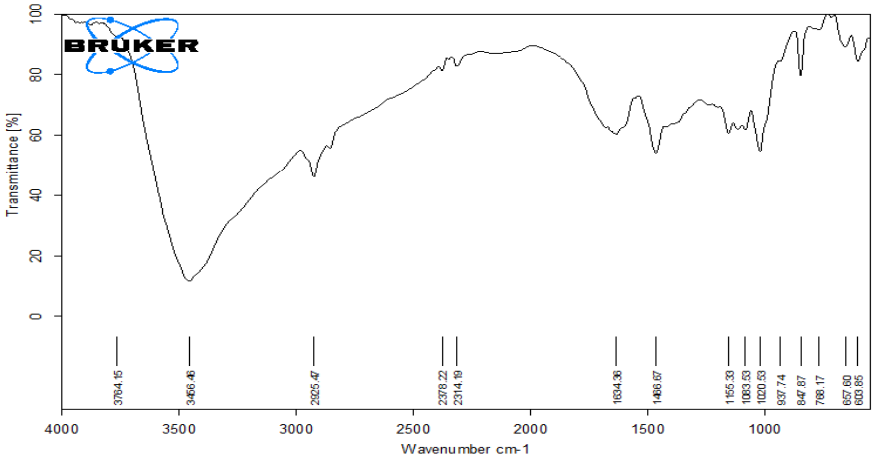

Fig. 2: Fourier transform infrared spectra of starch xanthate.

EVALUATION OF TABLETS

Hardness

The hardness of tablets from all batches was found to be in the range of 3.6±0.03 kg/cm2 to4±0.01 kg/cm2. All tablets were found hard enough so that they could easily withstand thehandling and storage conditions without getting broken.

Friability

All the tablets exhibited acceptable friability as none of the tested batches showed percentage friability that exceeded 1%. The percent friability of all batches found in the range of0.12%-0.15% indicating good mechanical resistance of tablets. Thus, it was proved that tablets could withstand the pressure, mechanical shocks during handling, transportation, storage and manufacturing processes.

Drug content

Drug content of all the formulation batches was found to be between 97.34±0.71 to 99.83±0.56.Hence, it can be concluded that all the formulations are having an accurate amount of drugdistributed uniformly in powder mass and followed acceptable limits as per IP.[14] i.e. 85 to 115% of average content table 3.

Disintegration studies

In vitro disintegration time was done by the USP dissolution apparatus. The disintegration rate has a correlation with water absorption capacity of disintegrate and The *In vitro* disintegrationtime was found between 12±0.02 to 312±0.02s. The outcomes were tabulated and datademonstrated in table 3. All the formulation showed disintegration time of less than 180s. It wasfound that the formulation F5 will show least disintegration time 12s as compare to otherformulation. The order for a disintegration time in the fast dissolving tablet was found to beF5<F6<F7<F8<F3<F4<F2<F1<F9. The order of disintegration time may be due to the interactionand main effects of the super disintegrants used in the fast dissolving tablets.

Water absorption ratio and wetting time

The water absorption ratio founded from 16±0.16 to 174±0.21s. This increased behavior due tothe water taking the ability of super disintegrants. The wetting time found between 76±0.21 to217±0.17s. The outcomes were tabulated and data demonstrated in table 3 and ig. 8, 8a and 8b.It was found that the formulation F5 containing 5 % starch xanthate and 5 % croscarmellosesodium showed less wetting time i.e. 76±0.21s as compared to other formulations.

***In vitro* dissolution studies**

Dissolution rate depends on the wetting time of the disintegrant, among all the formulations F8 has less wetting time and has greater dissolution rate and then this is the other conformance test for correct selection of desirable. *In vitro* dissolution studies of all the formulation were done and depicted in fig.6.4. In all formulations F8 formulation was selected as the promising formulation containing 5 % stach xanthate, 5% crospovidone and 5 % croscarmellose sodium with 99.15% release in 15 min which may be due to the interaction effect between the two super disintegrants i.e., Starch xanthate, crospovidone and croscarmellose sodium at a concentration of 5 % each. The dissolution parameters of the formulation from (F1– F8) which were made by direct compression method were shown in the table 1. In all these cases the PD5 (percent dissolved in 5 minute) was more in F8 which consists at 5 % Starch xanthate,5% crospovidone and 5 % croscarmellose sodium. The same was in the case of DE5 % (dissolution efficiency in 5 min). The PD5 & DE5 % revels that Starch xanthate was effective at 5%, crospovidone at 5% along with 5 % croscarmellose sodium when the formulations were made by direct compression using these superdisintegrants.

CONCLUSION

The enhancement of dissolution rate and oral bioavailability of poorly soluble drugs remains one of the most challenging aspects of drug development. In the present investigation, studies were carried out on optimization of fast dissolving tablets employing novel super disintegrate by direct compression method.

REFERENCES

1. R. Pahwa andN.Gupta, "Superdisintegrants in the development of orally disintegrating tablets: areview," *International Journal of Pharmaceutical Sciences and Research*, 2011; 2(11): 2767–2780.
2. D. Bhowmik, B. Chiranjib, P. Krishnakanth, and R. M. Chandira, "Fast dissolving tablet: an overview,"*Journal of Chemical and Pharmaceutical Research*, 2009; 1(1): 163–177.
3. P. Sehgal, R.Gupta, S.U. Kumar, C. Ashwani, G. Ashwini, and S. Mansi, "Fast dissolving tablets: anew venture in drug delivery," *The American Journal of PharmTech Research*, 2012; 2(4): 252–279.
4. M.Mangal and N. Thakur, "Fast dissolving tablets: an approach for emergency treatment," *International Research Journal of Pharmacy*, 2012; 3: 377–380.
5. K. Gaur, L. K. Tyagi, M. L. Kori, C. S. Sharma, and R. K. Nema, "Formulation an characterization offast disintegrating tablet of Aceclofenac by using sublimation method," *International Journal ofPharmaceutical Sciences and Drug Research*, 2011; 3(1): 19–22.
6. U. Kulkarni, N. G. Raghavendra, R. C. Hariprasanna, G. Rabbani, and B. S. Patil, "Formulation anddevelopment of Aceclofenac fast dissolving tablets-effect of functionality of subliming agents," *Journalof Applied Pharmaceutical Science*, 2011; 2(3): 179–190.
7. S. Chakraborty, M. Khandai, S. P. Singh, and N. C. Patra, "Comparative study on effect of natural andsynthetic superdisintegrants in the formulation of fast dissolving tablets of Aceclofenac," *International Journal of Green Pharmacy*, 2008; 2(1): 22–25.
8. A. H. Vadher, J. R. Parikh, R. H. Parikh, and A. B. Solanki, "Preparation and characterization of cogrinded mixtures of Aceclofenac and neusilin US2 for dissolution enhancement of Aceclofenac," *AAPS PharmSciTech*, 2009; 10(2): 606–614.
9. V. Sharma and V. Arora, "Comparison of various natural superdisintegrants in the formulation of fast

dissolving carvedilol tablet," *International Journal of Pharmaceutical Sciences and Research*, 2012; 3(10): 3947–3954.

10. K. Srinivas, K. Prakash, H. R. Kiran, P. M. Prasad, and M. E. B. Rao, "Study of *Ocimum basilicum* and *Plantago ovata* as disintegrants in the formulation of dispersible tablets," *Indian Journal of Pharmaceutical Sciences*, 2003; 65(2): 180–183.
11. Y. Bi, "Preparation and evaluation of a compressed tablet rapidly disintegrating in the oral cavity,"*Chemical and Pharmaceutical Bulletin*, 1996; 44(11): 2121–2127.
12. Y. X. Bi, H. Sunada, Y. Yonezawa, and K. Danjo, "Evaluation of rapidly disintegrating tablets prepared by direct compression method," *Chemical and Pharmaceutical Bulletin*, 1996; 44: 2121–2125.
13. M. K. Modasiya, I. I. Lala, B. G. Prajapati, V. M. Patel, andD.A. Shah, "Design and characterization of fast disintegrating tablets of piroxicam," *International Journal of PharmTech Research*, 2009; 1(2): 353–357.
14. S. B. Shirsand, S. Suresh, M. S. Para, P. V. Swamy, and D. N. Kumar, "Plantago ovata mucilage in the design of fast disintegrating tablets," *Indian Journal of Pharmaceutical Sciences*, 2009; 71(1): 41–45.
15. S. B. Shirsand, S. Suresh, and P. V. Swamy, "Formulation design and optimization of fast dissolving clonazepam tablets," *Indian Journal of Pharmaceutical Sciences*, 2009; 71(5): 567–572.
16. S. Shailesh and D. G. Ghanshyam, "Development and optimization of fast-dissolving tablets of promethazine theoclate using vacuum drying technology by 3-factor, 3-level response surface full factorial design," *Der Pharmacia Lettre*, 2010; 2(6): 124–135.
17. R. Kumar, S. Patil, M. B. Patil, S. R. Patil, and M. S. Paschapur, "Isolation and evaluation of disintegrant properties of fenugreek seed mucilage," *International Journal of PharmTech Research*, 2009; 1(4): 982–996.