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Research Article

PREPARATION AND EVALUATION OF ORODISPERSIBLE TABLETS OF FINASTERIDE USING CO-PROCESSED EXCIPIENTS

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ABSTRACT

Finasteride is a drug approved for the treatment of benign prostatic hyperplasia and male pattern baldness. It is a type II 5α-reductase inhibitor. 5α-reductase is an enzyme that converts testosterone to dihydrotestosterone.

Objective: The objective of this research was to formulate orodispersible tablets of Finasteride (FIN) to improve the patient compliance

Methods: Direct compression method was adapted to prepare the tablets by using mannitol,

microcrystalline cellulose(MCC PH102) and aerosile as filler, croscarmellulose sodium (CCS),

sodium starch glycolate (SSG) and crospovidone(CP) as superdisintegrants. Ten formulations were prepared and evaluated for flowability, hardness, friability, weight variation, content uniformity, wetting time, disintegration time and *in vitro* drug release. Co-processed excipient was prepared by solvent evaporation method includes combination of two superdisintegrants or MCC with Aerosile and mannitol. The developed excipient was characterized by differential scanning calorimetry (DSC) and Fourier Transform Infrared (FTIR) spectral study.

Results: Based on the results, formulation F10 contains 5% CP with co-processed granules of MCC with Aerosile and mannitol shows the best orodispersible properties regarding flowability, hardness and *in vitro* disintegration time (9.7±0.1sec)

Conclusion: This study it clearly indicated that the physical modification of the excipients by co-processed technique resulted inconsiderable improvement in its functionality as directly compressible material**,** thus formula (F10) consider promising to prepare stable orodispersible tablets of Finasteride with optimum properties

Keywords: Finasteride, Co-processed excipients, Orodispersible tablet

INTRODUCTION

Still today, oral drug delivery is the most favoured route for administration of various medications and is the most widely accepted [1]. A tablet has numerous advantages over other oral dosage form, among which are simplicity, low cost, speed of production, patient convenience and stability of a drug substance [2]. One of the important drawbacks of solid dosage forms is the difficulty in swallowing (dysphagia) or chewing for some patients particularly pediatric and geriatric patients. To overcome this weakness, innovative drug delivery systems have developed known as fast dissolving tablets or orodispersible tablets (ODTs). Fast disintegrating tablet of the type of those intended to undergo disintegration in the mouth in contact with the saliva in less than 40 seconds. Their characteristic advantages such as administration without water, anywhere, anytime lead to their suitability to geriatric and pediatric patients, they are also suitable for the mentally ill, the bedridden and patients who do not have easy access to water and also the bioavailability of drug is significantly greater than those observed from conventional tablet dosage form[3].

Finasteride(FIN) is a synthetic 4-azasteroid, a potent and specific inhibitor of steroid 5α-reductase, an intracellular enzyme that converts testosterone to dihydrotestosterone. It is used for treatment of benign prostatic hyperplasia, prostate cancer and male pattern baldness. FIN is rapidly absorbed from the gastro intestinal tract with peak plasma concentrations achieved within two hours [4, 5].

Co-processing is based on the novel concept of two or more excipients interacting at the sub particle level, the objective of which is to provide a synergy of functionality improvements as well as masking the undesirable properties of individual excipient . Co-processed excipient are prepared by incorporating one excipient into the particle structure of another excipient using processes such as co-drying[6]. Co-processing excipients leads to the formation of excipient granules with superior properties compared with physical mixtures of components or with individual components. Their characteristic advantages include absence of chemical changes, improved flow properties, improved compressibility and better dilution potential [7].

The object of this study was to formulate Finasteride ODT using direct compression technique and to clarify the effect of co-processing excipients and different superdisintegrants like Croscarmellose sodium (CCS),Crospovidone (CP), Sodium starch glycolate (SSG) on the disintegration and dissolution properties of tablets.

MATERIALS AND METHODS

Materials

FIN, Croscarmellose Sodium (CCS), Microcrystalline cellulose (MCC) PH 102 were obtained from Samarra Drug Industries (SDI), Iraq. Crospovidone (CP) and Sodium Starch Glycolate (SSG) were obtained from3B Pharmaceutical (Wuhan) International Co. Ltd. China. Colloidal silicon dioxide was obtained from Sigma-Aldrich, Germany.

Methods

Formulation of orodispersible tablets of Finasteride

The orodispersible tablets of FIN were prepared by direct compression technique using superdisintegrants (CCS, CP and SSG), mannitol as a diluent, aspartame as a sweating agent, colloidal silicon dioxide (Aerosil), Talc and Microcrystalline cellulose (MCC PH-102) as a flow promoter, Mg-stearate as a lubricant (Table 1). The drug (FIN) was mixed with the excipients (except the lubricant) for 15 minutes after which the lubricant was added and blended for another 1 minute. The final mixture was compressed using a 9-mm punch tablet machine**.**

Table 1: Composition of Finasteride Orodispersible Tablets

Material (mg)	F1	F2	F3	F4	F5	F6	F7	F8	F9	F10
FIN	5	5	5	5	5	5	5	5	5	5
CP	10	10	10	5	5*	5	5*	10	10	10
MCCPH 102		40	60					60	60	60*
CCS				5	5*					
SSG						5	5*			
Aerosile								2	4	2*
Aspartame	4	4	4	4	4	4	4	4	4	4
Talc	4	4	4	4	4	4	4	4	4	4
Mg stearate	2	2	2	2	2	2	2	2	2	2
Mannitol up to	200	200	200	200	200	200	200	200	200	200*

*****Excipients included in preparation of co-processed granules

Preparation of Co-Processed Excipients

Co-processed excipients were prepared by solvent evaporation method. In which10 ml of ethanol was added to a blend of excipients with continuous stirring till most of ethanol evaporated, the wet coherent mass was granulated through sieve no. 14.

The wet granules were dried in a hot air oven at 60˚C for 20 minutes and then the dried granules were sifted through sieve no. 14 and stored in air tight container till further use [8].

Evaluation of Co-Processed Excipients

Differential scanning calorimetry study

Differential scanning calorimetry (DSC) was used to characterize the co-processed excipients granules.

Approximately 2 mg of sample was taken in aluminium pan, sealed with aluminium cap and kept under nitrogen purging (atmosphere). The sample was scanned from 50-300 °C with the scanning rate of 20°C rise/min using differential scanning calorimeter (DSC-60, Shimadzu, Japan). An empty pan was used as a reference.

Fourier transforms infrared (FTIR) spectral study

Fourier transform infrared (FTIR) spectral study was done to find out the chemical stability or interaction of the excipients. FTIR spectra of co-processed excipients, and physical mixture in the same ratio were obtained. Spectral scanning was done in the range between 4000-400 cm^{-1}.

Evaluation of the Prepared Orodispersible Powder

Angle of repose

The angle of repose was measured by passing the prepared granules through a glass funnel of internal diameter 27mm on the horizontal surface. The height (h) at the heap formed was measured with a cathetometer, and the radius(r) of the cone base was also determined [9]. The angle of repose (Θ) was calculated the following equation.

$\tan \Theta = h/r$

Compressibility (Carr's) index

An accurate weight of formula granules was poured into a volumetric cylinder to occupy a volume (V_o) and then subjected to a standard tapping procedure onto a solid surface until a constant volume was achieved (Vf). The Carr's index was calculated using the following equation [9].

Compressibility Index = $(V_o - Vf)/V_o$

Evaluation of the prepared orodispersible tablets

Weight Variation

Randomly, 20 tablets were selected after compression and the mean weight was determined. The weight of not more than two tablets deviate from the average weight by no more than 7.5% and no tablet deviates by more than 15% [10].

Uniformity of content

The content uniformity of the prepared FIN orodispersible tablets was performed by taking ten tablets and assayed individually. The requirement for this test is met if the amount of ingredient in each of the ten tablets lies within the range of (85-115) % of the label claim [10]. The assay for drug was done using HPLC method. The HPLC system includes; Column: 5 µm C_{18} column, mobile phase: a filtered and degassed mixture of acetonitrile and water (29:21), flow rate: 2.0 ml/min, detection: UV-220 nm, injection volume: 100 µl and the retention time was found to be 2.5min [11].

Hardness

The crushing strength of the tablets was measured using a Monsanto hardness tester. Three tablets from each formula were tested randomly and the average reading± SD was recorded.

Friability

Ten tablet were weighed (w_o) and placed in a Roche friabilator and the equipment was recorded at 25 rpm for 4min.The tablets were taken out, dedusted, and reweighed(w)[12]. The percentage friability of the tablets was calculated using the following equation.

% friability = $(W_o - W)/W_o \times 100$

Wetting Time

The wetting time (WT) of tablets was measured using a simple procedure. A filter paper folded twice was placed in a small petri-dish (Internal diameter = 6 cm) containing 6 ml of artificial saliva at 25ºC.

A tablet was placed on the filter paper and the time required for the complete wetting of the tablet was recorded as a wetting time. The mean of three determinations was used ± SD[13,14].

In Vitro Disintegration Test

The disintegration tests were done for all formulas by using the USP disintegration apparatus, the basket rack assembly containing six open ended tubes and 10- mesh screen on the bottom was used, and the six tubes are filled with artificial saliva instead of water in order to simulate the *in vivo* environment as much as possible. The time in seconds required for complete passing of all fragment of the tablet is recorded as disintegration time of the tablet [15].

In Vitro Dissolution Studies

In vitro dissolution studies were performed by using type II (paddle) dissolution apparatus at 50 rpm, and 900 ml of water, as a dissolution medium. The dissolution apparatus was covered to protect the solution from light, and the temperature of dissolution medium was maintained at 37 ± 0.5°C [16]. Five ml aliquot of the dissolution medium was withdrawn at specific time intervals and replaced with 5 ml of the water and the percent of drug dissolved was determined using HPLC method previously described.

Stability studies

The stability study was carried out for the selected formula (F10). The tablets were stored at 40±2ºC/75±5% relative humidity (RH)

using stability chamber for 3 month, and then the samples were evaluated for various physical tests and drug release study [17].

Statistical Analysis

The results of the experiments are given at least as a mean of triplicate samples ± standard deviation and were analyzed according to the one way analysis of variance (ANOVA) at the level of ($P < 0.05$).

RESULT AND DISCUSSION

The weight variation (percent weight within the pharmacopial limits of ±10% of the average weight) and content uniformity tests (99.75±0.2) of the prepared FIN orodispersible tablets complied with USP specification.

The result indicated that addition of MCC PH102 in ODTs formulas result in improvement of flow properties as shown in table (2). Also it appears that addition use of 30% MCC leads to a significant($p<0.05$) decrease in *in vitro* DT and wetting time (Table 3).This decrease in *in vitro* DT and wetting time is related to good wicking and absorbing capacities of MCC.

Tablets contain MCC are disintegrated rapidly due to the rapid passage of water into the tablets resulting in the instantaneous rupture of the hydrogen bonds [18].

Table 2: Pre-compression Evaluation Parameters of Finasteride Orodispersible Formulation Powder Mixture (mean ± SD, n =3)

Formula No	Angle of repose (°)	Carr's index	Flow character
F1	38.65 ±1.69	23.0 ±2.84	Fair and Passable
F2	30.96 ±1.12	19.5 ±1.90	Excellent and Fair
F3	35.07 ±2.10	25.5 ±1.30	Good and Passable
F5	43.45 ±2.20	28.2 ± 2.11	Passable and Poor
F5	32.20 ±1.57	16.6 ±1.10	Good and Fair
F6	36.29 ±2.30	32.1 ±1.04	Excellent and very poor
F7	36.36 ±1.17	22.8 ±1.90	Fair and Passable
F8	37.07 ±2.10	26.3 ±1.18	Fair and Poor
F9	39.28 ±1.43	26.2 ±1.90	Fair and Poor
F10	22.20 ±1.60	21.0 ±1.90	Excellent and Passable

The results of use of two superdisintegrant together in formulation show that an increase in the angle of repose of formula when CCS was used (F4) while addition of SSG (F6) reduced it, so it appears that CCS decreases the flowability of pre compression powder while SSG improves it. This could be attributed to the fact that both CP and SSG are free flowing powder so mixing them together improves the flow property of the whole blend, where this doesn't occur with CCS [19].

Regarding the compressibility, hardness and friability, there is a decrease in compressibility and hardness with increase in friability of F4and F6 compared with F1 because CP is highly compressible powder and also SSG is synthesized from native starch which decreases the hardness of tablets by weakened the bonds that holding the tablet constituents together.

Furthermore, WT and *in vitro* DT are high in comparison to formula (F1) (CP alone). This result is due to the type of disintegration mechanism, since the major mechanism of disintegration of CP is wicking while that for SCC and SSG is swelling, when combining any of them with CP, both mechanisms act simultaneously and this leads to increase in tablet size and elongating the path for total wetting of the tablet, this result increases the time for complete wetting of the tablet and so disintegration.

Table 3: Evaluation Parameters of Prepared Finasteride Orodispersible Tablets

Formula No	*In vitro* DT(sec)	Wetting time (sec)	Hardness (kg/cm²)	Friability %
F1	11.0±2.0	11.0±3.0	3.5±0.5	0.61
F2	12.7±1.3	8.75±0.2	3.5±0.2	0.83
F3	9.70±0.1	7.90±0.1	3.5±0.1	0.89
F4	600 ±2.7	77.0±2.0	3.2±0.5	0.77
F5	16.5±1.0	14.8±0.1	3.8±3.0	0.59
F6	13.1±0.3	20.0±0.5	3.1±0.5	0.87
F7	11.0±0.5	12.8±0.1	3.1±0.5	0.84
F8	8.00±0.2	13.0±0.2	3.5±0.9	0.67
F9	8.00±0.2	15.5±0.1	3.1±1.0	0.91
F10	9.70±0.1	15.0±2.0	3.7±0.1	0.59

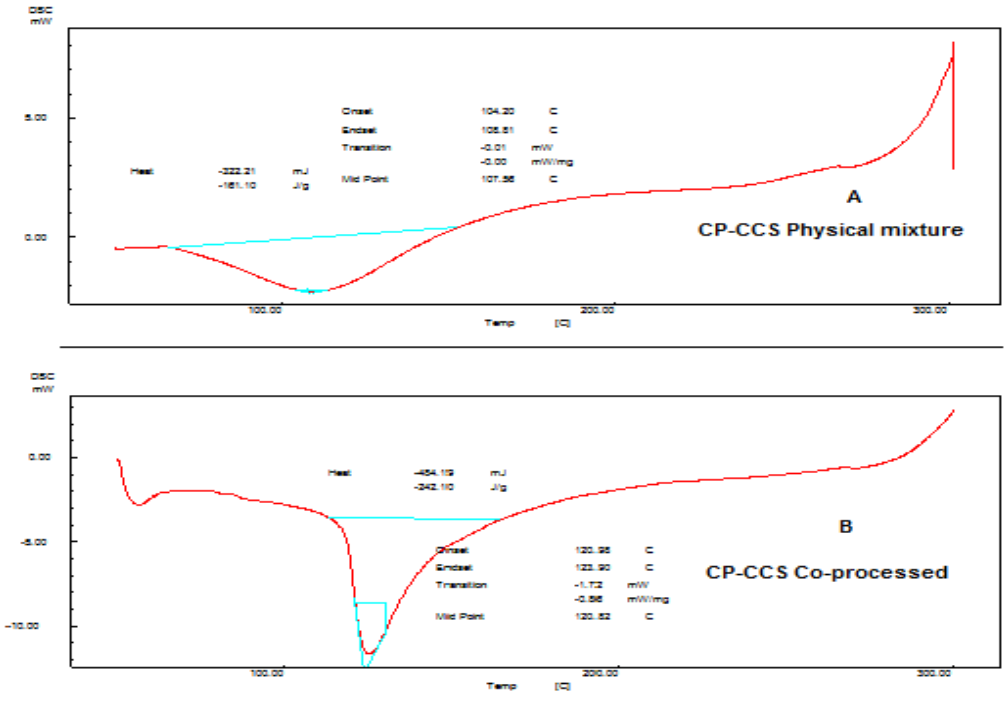

Fig. 1: DSC thermograms of (A) CP-CCS physical mixture, (B) CP-CCS co-processed granules

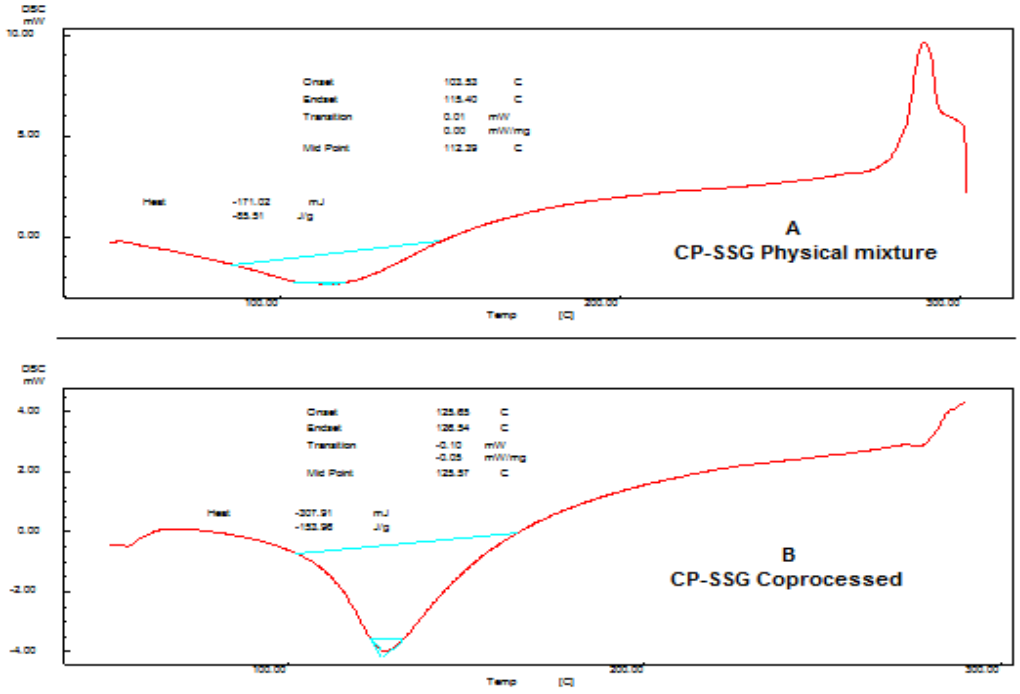

Fig. 2: DSC thermograms of (A) CP-SSG physical mixture, (B) CP-SSG co-processed granules.

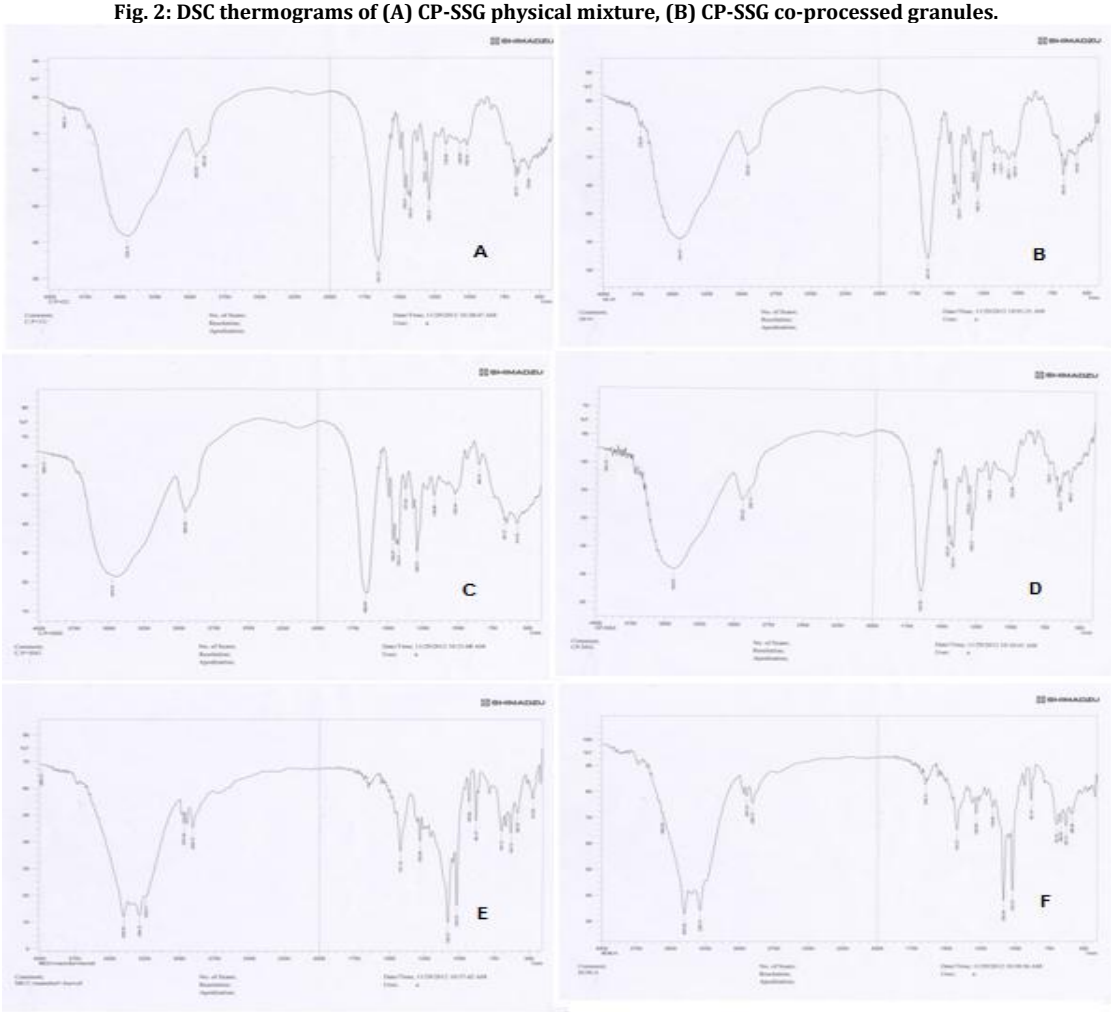

Fig. 3: FTIR spectra of (a) CP-CCS physical mixture, (b) CP-CCS co-processed, (c) CP-SSG physical mixture, (d) CP-SSG co-processed, (e) mannitol-MCC-aerosile physical mixture, (f) mannitol-MCC-aerosile co-processed.

Formula F5 and F7were utilized to investigate the influence of co-processed two superdisintegrants.

The thermogram of CP-CCS physical mixture showed a broad peak at 107.56°C, whereas the thermogram for CP-CCS co-processed granules recorded a highly intense peak at 120.82°C as shown in figure (1), also the thermal curve of CP-SSG physical mixture showed a broad peak at 112.39°C, whereas the thermogram for CP-SSG co-processed granules recorded a highly intense peak at 125.57°C as shown in figure (2) and these observations indicate that co-processed excipients technology lead to formation of new excipient with developed physical property [20]. The FTIR analysis of co-processed excipients as shown in figure (3) indicates no interaction since the characteristic peaks were not changed.

The result indicated that the formula contains co-processed excipient had better flow properties, and this is because the co-processed excipients had controlled particle size distribution which ensure superior flow properties [21]. In addition, the use of co-processed excipients leads to a significant decrease in *in vitro* DT and wetting time ($p<0.05$).This decrease is related to enlarging of the particle size, as particle size increased, particles became less cohesive.

The Addition of colloidal silicon dioxide (F8 and F9) resulted in a mild improvement of the flowability in case of 1% while worsening of the flow properties was observed with 2% and this may be due to poor flowability of colloidal silicon dioxide itself [22].

The co processing of excipients other than superdisintegrant is another approach to improve the properties of ODTs as in F10, mannitol with MCC PH 102 and aerosile were co-processed. It was found that the prepared co-processed granules had better flowability and compressibility [23], while there was slight increase in the *in vivo* DT, *in vitro* DT and wetting time (Table 3) and that might result from the increased hardness of F10 which leads to more cohesive particles. So the tablet was disintegrated slowly due to the slow passage of water into the tablets.

In vitro drug release studies (figure 4) shows significant enhancement of dissolution of FIN from the selected formula (F10) in comparison to the conventional tablets (Prosteride ®), this may be attributed to the effect of crospovidone that provides the fastest rate of dissolution of poorly soluble drugs and this will improve the drug release profile [24]. Moreover the stability study showed no significant difference ($p > 0.05$) in tablet properties after storage at 40ºC /75 ±5% RH for duration of three months.

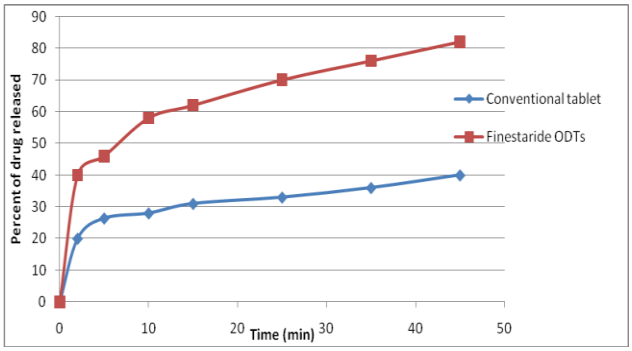

Fig. 4: Comparison of dissolution profile of selected formula (F10) to the conventional Finesteraide tablet

CONCLUSION

From the results of this study it can be concluded that the physical modification of the co-processed excipients resulted inconsiderable improvement in its functionality as directly compressible material that they exhibited improved flowability as measured by angle of repose and compressibility index. The salient points of the co-processed excipients are low cost, ease of availability of raw materials, quick disintegration of tablets and possibly regulatory acceptance. The overall results of this study indicate the possibility of utilizing the selected best formula (F10) in the preparation of FIN orodispersible tablets as a new dosage form for the oral administration.

REFERENCES

1. Chatur VM, Ghodekar SV, Kadam PM, Ratnaparkh MPi, Chaudhari SP. Quality evaluation of marketed formulation of mouth dissolving Voglibose tablets. International Journal of Pharmaceutical, Biological and Chemical Sciences. 2012;2: 01-04.
2. Allen L, Popovich N, Ansel H. Ansel's Pharmaceutical Dosage Forms and Drug Delivery Systems. 9th Edition. Lippincott Williams &wilkins, Philadelphia, USA. 2011: 225-256.
3. Anupama K, Shelly K, Neena B. Formulation and evaluation of mouth dissolving tablets of Oxcarbazepine. International Journal of Pharmacy and Pharmaceutical Sciences. 2009;1:12-23
4. Macek J. Separation of Finasteride and analogues. Journal of Chromatography B. 2001; 764: 207–215.
5. Gormley GJ. Finasteride: A Clinical Review. Biomed &Pharmacother 1995; 49: 319-324.
6. Gohel MC, Jogani PD. A review of co-processed directly compressible excipients. J Pharma Pharmaceutical Sciences. 2005; 8(1):76-96.
7. Alvaro Goyanes, Consuelo Souto, Ramón Martínez-Pacheco. Co-processed MCC-Eudragit® E excipients for extrusion–spheronization. European Journal of Pharmaceutics and Biopharmaceutics. 2011; 79: 658–663.
8. Ajay SC, Amrita D, Tushar T. Formulation development techniques of co-processed excipients. Journal of Advanced Pharmaceutical Sciences. 2012; 2(2): 231-249.
9. Tanmoy G, Amitava G, Devprasad. A review on new generation orodispersible tablets and its future prospective. Int J Pharmacy Pharm Sci. 2011; 3(1):1-7
10. Damodharan N, Mothilal M, and Vasundhara G, Formulation and optimization of fast dissolving cinnarizine tablets. International Journal of Pharmaceutical Technology Research, 2010;2(2):1095-1100.
11. United States Pharmacopoeia. Official Monograph. The USP convention.2007
12. Qureshi S. Tablet Testing. Encyclopedia of Pharmaceutical Technology. 2007; 3: 3707-3716.
13. Bhowmik D, Jaiswal J, Dubey V, Chandria M. Fast dissolving tablet: A Review on revolution of novel drug delivery system and new market opportunities. Scholars Research Library. 2009; 1 (2):262-276.
14. Fukami J, Yonemochi E, Yoshihashi Y, Terada K. Evaluation of rapidly disintegrating tablets containing glycine and carboxymethylcellulose. International Journal of Pharmaceutics. 2006; 310: 101-109.
15. Ramesh J, Reddy V, Rao G, Formulation and evaluation of oral disintegrating tablet of labetalol hydrochloride. International Journal of Pharmaceutical Science.2010;2(2) : 488-495.
16. Sharma S, Gupta G.D. Formulation and characterization of fast dissolving tablet of promethazine theocolate. Asian Journal Pharm. 2008; 70–72.
17. John R, Patel L. Stability testing of new drug substances and products. International Conference of Harmonization of Technical Requirements for Registration of Pharmaceuticals for Human use. 2003; 6:1-18.
18. Bayrak Z, Tas C, Tasdemir U, Erol H, Ozkan CK, Savaser A, Ozkan Y. Formulation of Zolmitriptan sublingual tablets prepared by direct compression with different polymers: In vitro and in vivo evaluation. European Journal of Pharmaceutics and Biopharmaceutics,2011 ;78:499–505.
19. Rowe RC, Sheskey PJ, Quinn ME. Hand book of Pharmaceutical excipients 6th edition, Pharmaceutical Press and American Pharmacists Association.2009.
20. Sanjay SP, Natvarlal MP. Development of directly compressible co-processed excipient for dispersible tablets using 3^2 full factorial design. Int J Pharmacy Pharm Sci., 2009; 1(1): 125-148.
21. Minakshi M, Deepak S, Rakesh KM. Coprocessing of excipients: A Review on excipient development for improved tabletting performance. International Journal of Applied Pharmaceutics.2010 ; (2) 3: 41-47.
22. Jonat S, Albers P, Gray A, Schmidt P. Investigation of the glidant properties of compacted colloidal silicon dioxide by angle of repose and X-ray photoelectron spectroscopy. European J. of Pharmaceutics and Biopharmaceutics. 2006;63(3):356-359.

23. Ornanong SK, Nisit K. Preparation and physicomechanical properties of co-precipitated rice starch-colloidal silicon dioxide. Powder Technology. 2012; 217: 377–382.

24. Balasubramaniam J, Bindu K, Rao VU, Ray D, Halder R, Brzeczko AW. Effects of superdisintegrants on dissolution of cationic drugs. Dissolution Technologies, 2008; 15(2):18-25.