Research Article

Effective Management of Rheumatoid Arthritis: An Approach for Bioavailability Enhancement of Flurbiprofen

Akhlesh Kumar Jain*, Ramakant Joshi, Parasuraman Mohan, Sunil K. Jain
School of Pharmaceutical Sciences,
Guru Ghasidas University, Bilaspur-495 009, INDIA

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Abstract

Objective: Present study aimed towards the development of a novel delivery system for pain management of rheumatic disorders. **Materials and methods**: An optimized solid dispersion (SD) of flurbiprofen was prepared using PEG 6000 at various ratios, of flurbiprofen and PEG 6000 i.e. 1:1, 1:2, 1:3, 1:4 and 1:5. The prepared SD formulations were optimized for solubility profile, Fourier Transform Infra-Red (FTIR) spectroscopy and differential scanning calorimetry (DSC). From IR, it may be concluded that there is change in crystalline form of drug into amorphous during formation of SD. From DSC studies, it was predicted that drug was completely dissolved in the carrier. Mouth dissolving tablets of flurbiprofen (MDTs) were formulated using optimized SD formulation of carrier: drug: polymer, (1:3) along with various super-disintegrants. **Results and discussion:** The developed batches of MDTs were characterized for micromeritic study, thickness, hardness, weight variation, wetting time, disintegration time, drug content and in vitro drug release profile. KT9 formulation containing 4% Kyron T-314 showed the best results with a wetting time and disintegration time of 28.3 and 38.3 sec, respectively. KT9 formulation showed superior drug release of 99.96% in comparison to 54.24% of conventional formulation over a period of 30 minutes. **Conclusion** Preliminary results from the study suggested that this Solid dispersion entrapped MDTs can be used to incorporate other anti arthritic drugs and could be effective against Rhematoid Arthritis.

Key words: Flurbiprofen, Kyron T-314, Mouth dissolving tablets, Solid dispersion, Rhematoid Arthritis

Introduction

About one-third of the world's population primarily the geriatric and pediatric patient have swallowing difficulties and mouth dissolving tablets (MDTs) is materialized as a gorgeous substitute for that group of patient. MDTs disintegrate or dissolve very rapidly in mouth as they come into the contact with saliva, without any need of extra water. This unique asset of MDTs combines the advantages of both liquid and conventional oral dosage form. Rapid disintegration of MDTs within the oral cavity fosters pregastric absorption through buccal mucosa, pharyngeal mucosa and oesophagus. Due to this pregastric absorption first pass metabolism is bypassed and accounts for the enhanced bioavailability of the incorporated therapeutic agent. Additionally, the problem of dysphagia especially in paediatric and geriatric individuals is triumphed over by the development of MDTs (Van den Mooter et.al 2011). These exceptional possessions put the MDTs on the upper hand in comparison to conventional dosage forms in terms of enhanced the patient compliance with better safety and efficacy (Habibh et al 2000; Douroumis 2007).

Commonly used techniques to enhance dissolution and bioavailability of poorly water-soluble drug are micronization, the use of surfactant and the formation of solid dispersion (SD). Among these, SD approach has been broadly and effectively applied to improve the solubility, dissolution rates, and subsequently, the bioavailability of poorly water soluble drugs. Major hurdle of SD technology is requirement of large amount of carrier which may be in some cases more than 50% to 80% w/w (Okonogi and Puttipipatkhachorn 2006; Schachter and Xiong 2004; Sethia and Squillante 2004) .

Many carriers such as polyethylene glycol (PEG), polyvinylpyrrolidone (PVP, hydroxypropylmethylcellulose

**Address for Corresponding Author:*
Dr. Akhlesh Kumar Jain
Asst. Prof. (Pharmaceutics)
School of Pharmaceutical Sciences,
Guru Ghasidas University, Bilaspur-495 009, INDIA
E mail: akjain.ie@gmail.com

(HPMC), hydroxypropylcellulose, hydroxypropyl methylcellulose phthalate (HPMCP), Gelucires®, Eudragits® and chitosans have been widely used in order to improve the solubility and bioavailability of drugs (Damian et al., 2002; Nakamichi et al 2002).

Over the years, rheumatic disorders present a mammoth challenge for the health professionals, especially in geriatric population. Rheumatoid arthritis (RA) is an autoimmune disease characterized by joint inflammation accompanied with long lasting severe pain leading to joint destruction or disability. According to the literature reports, this disease markedly influences the population with a contributory percentage of 1% approximately. NSAIDs like ibuprofen, aspirin, naproxen and indomethacin are preferred for pain management in RA and acts by blocking prostaglandin synthesis owing to non selective inhibition of cyclooxygenase enzyme (COX-1 & COX-2) (Caughey et al 2001). The use of these therapeutic agents is restricted due to the associated severe GI distress and ulcers.

Flurbiprofen, a phenylpropionic acid derivative has analgesic, anti-inflammatory and antipyretic proficiency with proven efficacy for the pain management in RA in human being. Similar to other NSAIDs, the anti-inflammatory activity of flurbiprofen credited to reversible inhibition of COX, the enzyme responsible for the conversion of arachidonic acid to prostaglandin G2 (PGG2) and PGG2 to prostaglandin H2 (PGH2) in the prostaglandin synthesis pathway. This transformation effectively decreases the prostaglandins concentration responsible for inflammation, pain, swelling and fever. Low aqueous solubility and some serious abdominal side effects like GI irritation, GI bleeding etc. hold back the applications of this marvel NSAIDs member for treatment of RA. Its high lipophilicity with a log P value of 4.42 rationalizes its lower bioavailability after oral administration due to which frequent dosing is required (Brogden et al., 1979; Teixeira et al., 1984). These shortcomings may be conquered by the utilization of solubility enhancement technique i.e. solid dispersion and novel formulation approach i.e. MDTs.

The present course of study attempts to enhance the solubility of flurbiprofen by solid dispersion technique with polyethylene glycol (PEG 6000) and compressed it as a MDT in order to develop an effective treatment for the management of RA.

Materials and methods

Materials

Flurbiprofen was purchased from M/s Mahalakshmi Chemicals Hyderabad, India. Sodium starch glycolate, Croscarmellose sodium was a kind gift from Maple Biotech Pvt. Ltd. Pune, India and kyron T-314 was kindly donated by Corel Pharma Chem., Ahemdabad, India. Poly ethylene glycol (PEG 6000), Micro crystalline cellulose was purchased from SD fine chemicals; Mannitol, Magnesium stearate, and Talc were purchased from Himedia laboratories Ltd Mumbai. All other chemicals used were of analytical grade.

Preparation and characterization of solid dispersion

Solid dispersion of flurbiprofen and PEG 6000 was prepared using different ratios i.e. 1:1, 1:2, 1:3, 1:4, 1:5 by conventional solvent evaporation method (Sethia and Squillante, 2004). Briefly, flurbiprofen and PEG 6000 were weighed accurately in different ratios and mixed uniformly. This mixture was dissolved in ethanol with continuous

Table 1. Composition of various mouth dissolving tablets of flurbiprofen

S. No.	Ingredients (mg)	Formulations								
		SSG1	SSG2	SSG3	CCS4	CCS5	CCS6	KT7	KT8	KT9
1.	Solid dispersion (Eq. to 100 mg flurbiprofen)	400	400	400	400	400	400	400	400	400
2.	Sodium starch glycolate	10	15	20	-	-	-	-	-	-
3.	Croscarmellose sodium	-	-	-	10	15	20	-	-	-
4.	Kyron T-314	-	-	-	-	-	-	10	15	20
5.	Mannitol	25	25	25	25	25	25	25	25	25
6.	Microcrystalline cellulose (MCC)	56	51	46	56	51	46	56	51	46
7.	Magnesium stearate	4	4	4	4	4	4	4	4	4
8.	Talc	5	5	5	5	5	5	5	5	5
9	Total weight	500	500	500	500	500	500	500	500	500

stirring and subjected to solvent evaporation by heating at 40ºC. The resultant solid dispersions were dried for 24 hr in a desiccator. Dried mass was scraped, crushed, pulverized and passed through sieve (# 60) and stored until further use.

Solubility study

Samples (pure drug and solid dispersion) equivalent to 10 mg of flurbiprofen were added to 10 ml each of distilled water and PBS (pH 6.8). These dispersions were shaken well and kept for 24 h. The solution was filtered through whatman filter paper (#41) and analysed for drug content at 247 nm using UV-Visible spectrophotometer (UV-1800, Shimadzu, Japan).

Infrared spectroscopy

IR spectroscopy of flurbiprofen, PEG 6000 and their solid dispersion was performed on Fourier transform infrared spectroscopy (FTIR 8400S, Shimadzu, Japan). KBr (95:5) disk with Drug, carrier and solid dispersion was prepared separately with, placed in to sample holder and scanned over 400-4000 cm^{-1} scanning range.

Differential scanning calorimetry (DSC)

Differential scanning calorimetry (DSC) measurements was performed for flurbiprofen, PEG 6000 and its solid dispersion using DSC instrument (JADE DSC-6, PYRIS, USA) equipped with a liquid nitrogen sub ambient accessory. Samples of 2–6 mg were placed in aluminum pans (Al-Crucibles, 40 Al) and sealed. The probes were heated from 30 to 100°C at a rate of 5°C/min under nitrogen atmosphere. The temperature was calibrated using pure indium with a melting point of 156.6°C. An empty pan was used as a reference standard.

Drug content analysis

Accurately weighed quantity of solid dispersion (theoretically equivalent to 10 mg of flurbiprofen) was dissolved in small amount of ethanol and volume was made up to 10 ml with PBS (pH 6.8). The solution was sonicated for 5 min., filtered through whatman filter paper (#41) and assayed for drug content by UV-spectrophotometer (UV-1800, Shimadzu, Japan) at 247 nm.

Characterization of powder blend for MDTs

Micromeritic studies

The powder mixture of formulations was characterized for their micromeritic properties, such as bulk density, tapped density, compressibility index, angle of repose and hausner ratio. An accurately weighed quantity of the powder mixture of formulations was carefully poured into the graduated cylinder and volume was measured, which is called bulk volume, the graduated cylinder was closed with lid and set into the tap density tester. The density apparatus was set for 100 tabs, noted as tapped volume (Lachman et al., 2008). Bulk density, tapped density, % compressibility index and hausner ratios were calculated using following formulae:

$$Bulk\ density\ (BD) = W/V_0,\ and\ Tapped\ density\ (TD) = W/V_f$$

Where, W= Weight of the powder V_0= Initial volume, V_f= final volume

$$Carr's\ index\ (\%) = [(TD-BD) \times 100]/TD$$

Angle of repose of the powder was determined by the fixed funnel method. Angle of repose was calculated using the following equation given below:

$$Tan\ \theta = h/r$$

Where, h= Height of pile and r= Radius of the pile

Table 2. Micromeritic studies of various powder blend formulations prepared

Batch	Angle of repose	Bulk density	Tapped density	%Compressibility	Hausner ratio
SSG1	29.15±0.72	0.54±0.06	0.65±0.06	16.16±0.31	1.18±0.05
SSG2	27.63±0.73	0.53±0.05	0.64±0.01	16.38±0.53	1.19±0.01
SSG3	28.78±0.68	0.53±0.08	0.63±0.08	15.32±1.92	1.17±0.02
CCS4	27.46±1.04	0.52±0.05	0.65±0.09	19.51±1.95	1.23±0.03
CCS5	27.79±0.60	0.54±0.04	0.66±0.06	17.56±0.41	1.20±0.05
CCS6	28.77±0.88	0.54±0.07	0.63±0.06	14.99±2.04	1.17±0.02
KT7	28.83±1.43	0.52±0.04	0.63±0.07	17.86±1.62	1.21±0.02
KT8	26.52±1.24	0.54±0.08	0.64±0.08	15.67±0.38	1.18±0.05
KT9	26.36±0.34	0.52±0.02	0.65±0.08	19.49±1.20	1.23±0.02

Values are expressed as mean ± S.D., n=3

Table 3. Evaluation parameters of various mouth dissolving tablets prepared

Batch	Friability (%)	Hardness (kg/cm2)	Disintegration time (sec)	%Drug content
SSG1	0.71±0.02	3.43±0.05	94.0±4.58	95.42±0.36
SSG2	0.50±0.04	3.37±0.15	81.6±3.51	97.95±0.29
SSG3	0.63±0.01	3.35±0.21	71.3±1.52	98.31±0.08
CCS4	0.58±0.07	3.42±0.17	76.6±2.08	96.26±0.56
CCS5	0.60±0.23	3.65±0.22	68.6±2.08	98.79±0.74
CCS6	0.63±0.23	3.72±0.06	58.6±1.52	99.63±0.11
KT7	0.63±0.04	3.26±0.11	56.3±1.52	97.46±0.31
KT8	0.55±0.07	3.53±0.08	44.6±1.50	96.02±0.04
KT9	0.46±0.18	3.62±0.14	38.3±2.08	98.67±0.28

Values are expressed as mean ± S.D., n=3

Formulation of mouth dissolving tablets using solid dispersion

The solid dispersion formulation containing 1:3 ratio is selected for tablet preparation on the basis of solid dispersion characterizations i.e. solubility, FTIR, DSC, and drug content. Direct compression technique was utilized for the compression of solid dispersion of flurbiprofen and PEG 6000 for the development of MDTs. All ingredients (solid dispersion equivalent to 100 mg flurbiprofen and other excipients) were mixed properly and the blends were passed through sieve (# 40). The powder blend was compressed into tablets on a single punch tablet machine using round shape flat punch having diameter of 12 mm (Rolex machineries, Mumbai, India). The tablet weight was adjusted to 500 mg (Table 1). Sodium starch glycolate, croscarmellose sodium and kyron T-314 were used as super disintegrating agent. While microcrystalline cellulose (MCC), magnesium stearate were used as diluents and as lubricant, respectively.

Evaluation of mouth dissolving tablets

Thickness, hardness, Friability and weight variation

The crushing strength (hardness) was determined using a Monsanto hardness tester (Sheetal Scientific Industries, Mumbai, India). The tablet geometry was determined by a means of a micrometer (Baty Co., Ltd, England). Initial weight of the 10 tablets was measured and subsequently placed in chamber of friabilator (Roche friabilator) and rotated for 100 revolutions. After that tablets were de-dusted, reweighed and % friability was calculated. From each batch twenty tablets weight were noted using and average weight (W_A) was calculated. Percentage weight variation and average weights of the tablets along with standard deviation values were calculated using formulae given below.

$$\% \text{ Weight variation} = (W_A - W_T)/W_A$$

Wetting time

Ten mL of water containing eosin, a water- soluble dye, was added to Petri dish. A tablet was carefully placed on the surface of the tissue paper. The time required for water to reach upper surface of the tablet is noted as wetting time (Ghoel et al 2004).

Disintegration time

Disintegration test was performed using USP device comprises of six glass tubes that are 3" long, open at the top, and held against 10" screen at the bottom end of the basket rack assembly. One tablet is placed in each tube and the basket rack is positioned in a beaker containing 900 ml of PBS (pH 6.8) at 37±2°C, such that the tablets remain below the surface of the liquid on their upward movement and descend not closer than 2.5cm from the bottom of the beaker. The disintegration time was recorded at the point at which tablet completely disintegrated.

Drug content

Ten tablets were weighed, crushed and powdered. An amount of the powder equivalent to 10 mg of flurbiprofen was dissolved in 100 ml of phosphate buffer pH 6.8, filtered, diluted suitably and analyzed for drug content at 247 nm using UV spectrophotometer (UV-1800, Shimadzu, Japan).

In vitro drug release study and Release kinetics

The i*n vitro* drug release of all formulations was studied by using six rotating paddle apparatus (USP Dissolution apparatus II, Electrolabs, Mumbai). Each tablet was placed in the paddle dissolution assembly containing 900 ml of phosphate buffer (pH 6.8). The paddle was rotated at 100

Table 4. Release kinetics of various mouth dissolving tablets prepared

Formulations	Zero order	First order	Higuchi kinetic	Hixson-Crowell kinetic	Korse Meyer-Peppas kinetic	
	R^2	R^2	R^2	R^2	R^2	N
SSG1	0.587	0.885	0.698	0.777	0.778	0.151
SSG2	0.956	0.959	0.991	0.991	0.997	0.121
SSG3	0.923	0.930	0.974	0.986	0.992	0.105
CCS4	0.971	0.918	0.969	0.967	0.947	0.124
CCS5	0.983	0.954	0.987	0.977	0.989	0.242
CCS6	0.978	0.938	0.975	0.963	0.987	0.516
KT7	0.945	0.992	0.978	0.984	0.980	0.492
KT8	0.973	0.928	0.979	0.968	0.978	0.412
KT9	0.999	0.654	0.988	0.972	0.968	0.136

rpm and temperature of dissolution medium was thermostatically controlled at 37± 0.5°C. Samples were withdrawn at different intervals, diluted suitably and analyzed at 247 nm for cumulative drug release using UV spectrophotometer (UV-1800, Shimadzu, Japan

Release kinetic models like zero order (Eq. 1), first order (Eq. 2), Higuchi matrix (Eq. 3), Peppas-Korsmeyer (Eq. 4) and Hixon-Crowell (Eq. 5) were applied to in vitro drug release data of tablets to find the equation with the best fit (James et al 1997; Wu et al 2002). (1)

$$R = k_1 t \quad (1)$$

$$\log UR = \frac{k_2 t}{2.303} \quad (2)$$

$$R = k_3 t^{0.5} \quad (3)$$

$$R = k_4 t^n \quad (4)$$

or

$$\log R = \log k_4 + n \log t$$

$$(UR)^{1/3} = k_5 t \quad (5)$$

Where R and UR are the released and unreleased percentages, respectively, at time (t); k_1, k_2, k_3, k_4 and k_5 are the rate constants of zero order, first order, Higuchi matrix, Peppas Korsmeyer and Hixon-Crowell model, respectively. The coefficient of correlation (R^2) values were calculated from the regression analysis of above plots.

Results and discussion

Solubility study

The solubility, of pure drug in water is reported to be 7.85 µg/ml which, suggest that flurbiprofen is practically insoluble in water, hence shows lower bioavailability. In present study solid dispersion of flurbiprofen was prepared with various ratios of PEG 6000 i.e. 1:1, 1:2, 1:3, 1:4, and 1:5. The solubility of these

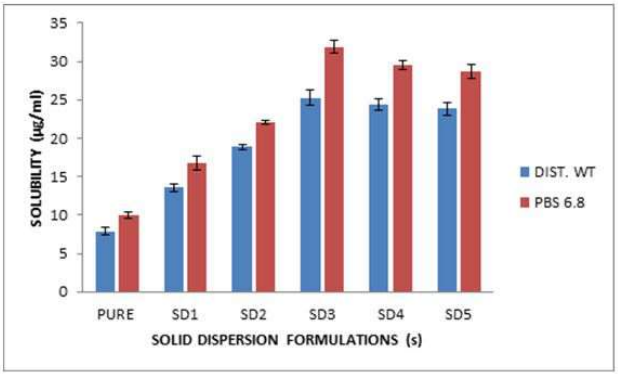

Figure 1. Solubility Profile of various solid dispersions prepared in distilled water and PBS (pH 6.8).

dispersions were found to be 16.74, 22.12, 31.88, 29.51, and 28.67 µg/ml in PBS (pH 6.8) respectively (Figure 1). Flurbiprofen is completely miscible in PEG 6000 so that it converted from crystalline to amorphous form. Result suggests that solubility of flurbiprofen is increased with respect to the concentration of PEG 6000 till 1:3 (4 folds compared to pure drug) and it started decreasing thereafter. (Reddy et al., 2013). Developed MDTs of domperidone solid dispersion by solvent evaporation method using PEG 6000. They reported 2.44 folds solubility enhancement with respect to pure domperidone. Another research group prepared solid dispersion of PEG 6000 and enhanced solubility and dissolution rate of etoposide by 1.86 folds in comparison of pure drug(Shah et al 1995) .

Infrared spectroscopy

In order to get evidence on the possible interaction of the drug with carrier, FTIR was used. The FTIR spectra of drug shows characteristic bands of C=O stretching at 1691.57

cm^{-1}, O-H stretching of acidic group at 3369.64 cm^{-1}, C-F stretching at 1128.36 cm-^{1}(Figure 2). The spectrum of PEG 6000 shows, important bands of C-H (aromatic ring) stretching at 2883.58 cm^{-1}, C=C (aromatic ring) stretching at 842.89 cm^{-1} and C-O (ether) stretching at 1109.07 cm^{-1}. The change in the position of C=O vibration occurs which appear at 1693.50 cm^{-1} and disappearance of O-H stretching, when flurbiprofen was dispersed in PEG 6000. The absorption band at 3369.64 cm^{-1} is assigned to O-H stretching because of intermolecular association appeared to decrease, by increase the amount of PEG 6000. Solid dispersion brings characteristic change in the flurbiprofen from crystalline to amorphous by dispersing it into PEG 6000, which leads to solubility enhancement and improvements of flow properties.

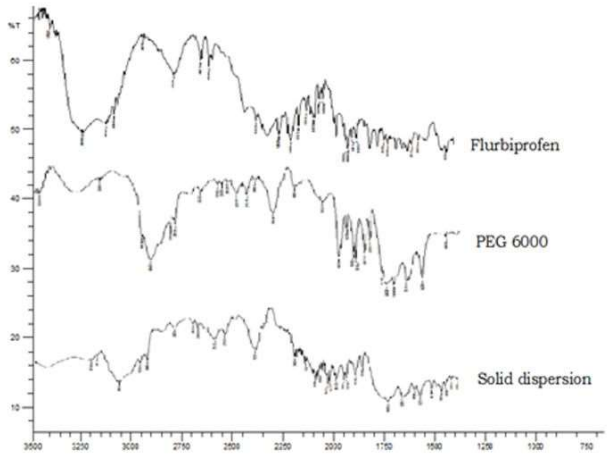

Figure 2. Fourier transform infrared (FTIR) spectra of Flurbiprofen, PEG 6000, and solid dispersion

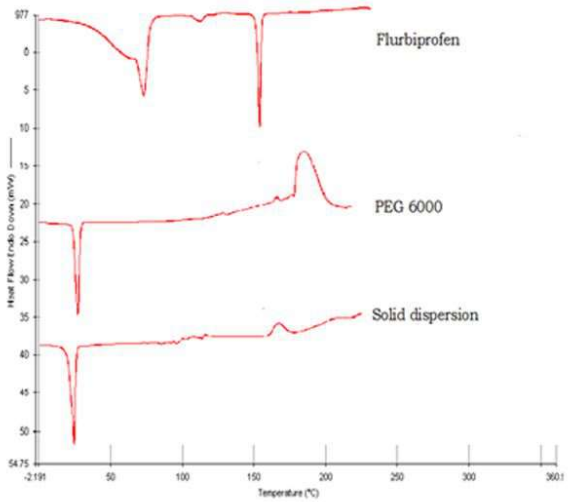

Figure 3. Differential scanning calorimetry (DSC) thermogram of flurbiprofen, PEG 6000, and solid dispersion (30-350^{0}C) at 10^{0}C/min

Differential scanning calorimetry (DSC)

DSC thermograms of the (a) FLUR, (b) PEG 6000, (c) Solid dispersion are shown in (Figure 3). The DSC thermogram of flurbiprofen exhibited an endothermic peak at 118.03^{0}C, which corresponds to the melting point of the flurbiprofen. The carrier PEG 6000 showed an endothermic peak at 63.06^{0}C, which corresponds to the melting point of PEG 6000. There were only one endothermic peak observed for solid dispersion prepared using drug:carrier 1:3 at 58.06^{0}C. The disappearance of endothermic peak at the melting point of flurbiprofen in solid dispersion gives an idea that flurbiprofen might being present in dissolve state in melted PEG 6000. This could be attributed to higher PEG 6000 concentration and uniform distribution of drug in the crust of PEG 6000 resulting in complete miscibility of molten drug in PEG 6000. The disappearance of endothermic peak in solid dispersion formulations confirms the amorphous state of drug in prepared solid dispersion formulations.

Formulation of MDTs using solid dispersion

From above studies it was found that solid dispersion ratio SD3 (1:3) has maximum solubility and drug content, is selected for further preparation of MDTs with Superdisintegrants i.e. sodium starch glycolate, croscarmellose sodium and kyron T-314. Superdisintegrants were taken in various ratios to find the optimum concentration required to yield formulation having least wetting time and disintegration time.

Micromeritic studies

Micromeritic properties of powder reflect the appropriateness of formulation. Hence, micromeritic properties of the drug excipients mixture were studied in term of bulk density, tapped density, car's index and angle of repose to establish the flow property. The car's index of all the formulations was found to be in the range from 14.99 % to 19.51%. The hausner's ratio was found to be in the range from 1.17 to1.23 (i.e. less than 1.25), which indicates good flow properties. Angle of repose was found to be 26.36º to 29.15 º (Table 2). (Elkhodairy et. al., 2014) prepared orodispersible tablets of flutamide in which they found car's index 17.88% to 21.18% and hausner ratio 1.21 to 1.27. This indicates passable flow property. The angle of repose of their formulation powder was 30.1º to 45.48º. In comparison, these properties of flurbiprofen is very poor so it can not used for direct compression but the car's index of all formulations powder mixtures was found to be in the range from 14.99 % to 19.51%. The micromeritic properties of pure drug doesn't show the free flow of powder for compression but when the solid dispersion of the flurbiprofen is prepared with PEG 6000 and mixed with other excipients and evaluated for micromeritic properties shows free flowability and compressibility for direct compression. PEG 6000 alters the particle size and shape of

drug particles from crystalline to spherical resulting in enhancement of flowability and compressibility.

Evaluation of MDTs

Thickness, Hardness, Friability and weight variation

All the prepared tablets were characterized by their size and shape, which found round shape and uniform thickness in the range of 4.13 to 4.56 mm (Data is not shown). The hardness of formulations was found within the range of 3.26 to 3.72 kg/cm^2 (Table 3). Friability for all formulations was found to be less than 1%, which is within the acceptable limit. The result shows resistance to loss of weight indicated the tablet ability to withstand abrasion in handling, packaging and shipment. The weight uniformity met USP specification of less than ± 5% variation. (Data is not shown).

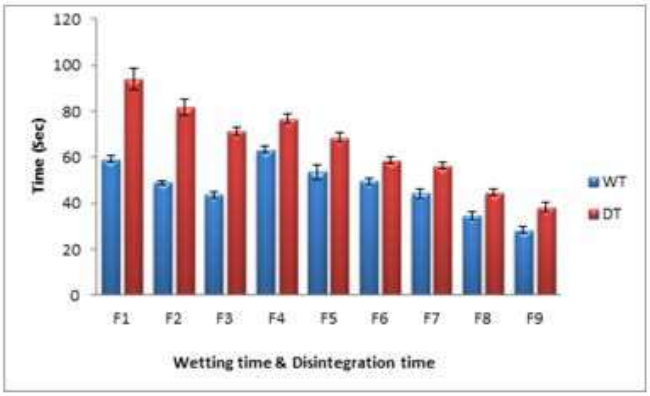

Figure 4. Wetting time & Disintegration time of various mouth dissolving tablet formulations prepared

Wetting time

Wetting time for MDTs depends on the concentration of superdisintegrants. Three types of superdisintegrants i.e. sodium starch glycolate (SSG), croscarmellose sodium (CCS) and kyron T-314 in the concentration range of 2 to 4%. The wetting time for all formulations was 59.3 to 43.6 sec for SSG containing formulation, 63.3 to 49.6 sec for CCS containing formulation, and 44.3 to 28.3 sec for kyron T-314 containing formulation. The least wetting time amongst all formulation is found with KT9 formulation which contains 4% kyron T-314. Kyron T-314 is a crosslinked polymer of Polycarboxylic acids breaks the tablets into very smaller particles, thus it increases the effective surface area for the absorption of the active substances and ultimately it increases the dissolution and bioavailability of the active substances. Its 2.0 - 4.0% quantity is sufficient for dissolution improvement and suitable for direct compression. It also provide smooth cream-like mouth feel, so more suitable for MDTs. All the results of wetting time of all formulations are shown in Figure 4 (Singh and Shah et al) prepared MDTs of zolmitriptan by direct compression using sodium starch glycolate, croscarmellose sodium, kyron T-314, and crospovidone in which they found wetting time 38 sec, 59 sec, 40 sec, and 31 sec, respectively with these superdisintegrants at 4% concentration. In comparison of that wetting time of prepared tablets decreased with an increase in the level of kyron T-314 (2%-4%) i.e. 44.3 to 28.3 sec. Since kyron T-314 has a very high swelling tendency of hydration either in contact with water or G.I. fluids causing very fast wetting of the tablets.

Drug content

Percentage drug content of various formulations i.e. SSG1, SSG2, SSG3, CCS4, CCS5, CCS6, KT7, KT8 & KT9 were found to be 95.42%, 97.95%, 98.31%, 96.26%, 98.79%, 99.63%, 97.46%, 96.02% and 98.67% respectively. The percent drug content was found to be in the USP limits for all formulations. The % drug content for all formulations is represented in Table 3.

Disintegration time

Another fact of MDTs which is much more important is disintegration time of the tablets. According to European pharmacopoeia MDTs required less than 3 minute in disintegration. In the present study, all the developed tablets disintegrated in approximately 1.5 minutes. Disintegration time was found between 1.56 to 1.18 min for SSG containing formulation, 1.27 min to 58.6 sec for CCS containing formulation, and 56.3 to 38.3 sec for kyron T-314 containing formulation (Figure 4). MDTs of roficoxib was developed using 4 % (12 mg) sodium starch glycolate and crosscarmellose sodium and they showed disintegration time of 4.25 min and 3.05 min, respectively. (Sammour et al 2006). In comparison of that disintegration time of prepared tablets was decreased 1.56 to 1.18 min and 1.27 min to 58.6 sec with an increase in the level of sodium starch glycolate and crosscarmellose sodium (2% to 4%) respectively. In case of kyron T-314 it also decreased i.e. 56.3 to 38.3 sec with an increase in the level of kyron T-314. Among all superdisintegrants, kyron T-314 show faster disintegration time for tablets (for KT9 38.3 sec) this is because it has a very high swelling tendency of hydration either in contact with water or G.I. fluids causing fast disintegration without the formation of lumps and thus acts as an effective tablet super disintegrant. The porous structure of the tablets is responsible for faster water uptake resulting in fast disintegration.

In vitro drug release study

The cumulative percent drug release of formulations i.e. SSG1, SSG2, SSG3, CCS4, CCS5, CCS6, KT7, KT8 & KT9 were 98.31%, 97.44%, 99.19%, 98.41%, 90.22%, 80.21%, 84.71%, 91.40% & 99.96% respectively, in 30 minute (Figure 5). Elkhodairy et al., 2014 developed orodispersible tablets of flutamide in which they used

sodium starch glycolate (SSG) as a superdisintegrant. Formulation containing various concentration of SSG 5mg, 10mg, and 20mg shows 70.63%, 73.59% and 79.94% drug release respectively in 45 min. They also used solid dispersion with PEG 6000 which shows 100% drug release in 45 min. In comparison of that developed formulation SSG3 contains 20mg of SSG shows 99.19% drug release in 30 min. Another scientist evaluate the disintegration property of cross linked polymer using different superdisintegrants for aspirin and hydrochlorthiazide drug (Chang et al 1998). Aspirin tablet containing 1% croscarmellose sodium showed 90% drug release in 30 min. and hydrochlorthiazide tablet containing 1% croscarmellose showed 30% drug release in 30 min. In comparison of that our formulation CCS4 showed 98.41% drug release in 30 min. Also, another research group investigated disintegration property of rapid dispersible tablets of tolfenamic acid, in which they used 2% kyron T-314 which shows approximately 70% drug release in 30 min (Anand et al 2013). In comparison of that our formulation KT7 contain 2% kyron T-314 shows 84.71% drug release in 30 min. and formulation KT9 contains 4% kyron T-314 shows maximum drug release 99.96% in amongst all formulation prepared.

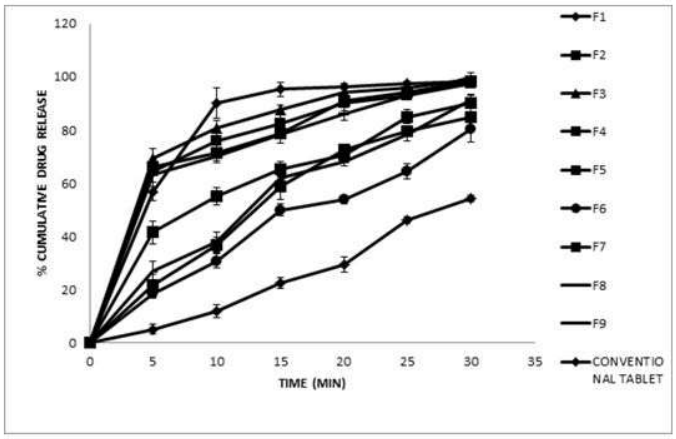

Figure 5. Cumulative % drug releases of various Mouth dissolving tablet formulations prepared at 37± 2ºC

The release of the formulation is also compared with conventional formulation and the plot of cumulative percentage release Vs time is drawn (Figure 5). The cumulative percent drug release of formulation i.e. SSG1, SSG2, SSG3, CCS4, CCS5, CCS6, KT7, KT8 & KT9 were 98.31%, 97.44%, 99.19%, 98.41%, 90.22%, 80.21%, 84.71%, 91.40% & 99.96% respectively in 30 minute, while the cumulative percent release for conventional formulation is only 54.24% in 30 minute. Formulation KT9 containing kyron T-314 shows better drug release profile 99.96%.

The in-vitro drug release profile of various optimized formulations were studied for release kinectics with respect to zero order, first order, Higuchi, Hixson crowell and Korsemeyer-peppas model (Table 4). The R^2 for various kinetics models for optimized formulation KT9 was found 0.999, 0.654, 0.988, 0.972, 0.968 respectively, which is closer to one, particularly for Zero order model. The diffusional exponent, n characterizes the mechanism of drug release. It is known that for non-swelling tablets, the drug release can generally be expressed by the Fickian diffusion mechanism, for which $n = 0.5$. For non-Fickian release, the n value falls between 0.5 and 1.0 [$0.5 < n < 1.0$]; whereas in the case super case II transport $n > 1$. The value of n for all formulations is in the range from 0.151 to 0.516. Which conclude that all formulation followed fickian diffusion mechanism.

Another aspect of formulations characterization was in vivo pharmacokinetic studies, which conclude the efficacy of the formulations. Researcher developed fast dispersible aceclofenac tablets in which they used PEG 6000 in 2.5% and 5% concentration. Results demonstrates that formulation containing 2.5% PEG 6000 show better results in terms of disintegration time 2.06 min, % drug release 94.95% in 60 mins. This formulation was used for in vivo studies and compared with marketed formulation shows C_{max} 1.04 times higher, where as T_{max} was 4 hr, AUC (Area under the curve) and AUMC was 1.18 times, 1.57 times more respectively (Shanmugapandiyan et al 2011). In comparison of that formulation containing 1:3 solid dispersion of PEG 6000 with kyron T-314 superdisintegrant shows 38.3 sec disintegration time and 99.96 % drug release in 30 mins. Based on these predictions pharmacokinetic study of formulations will show better bioavailability compare to marketed formulation. Another Researcher developed fast dissolving tablets of pioglitazone hydrochloride by solid dispersion using sodium starch glycolate (SSG) in various concentrations (Shanmugapandiyan et al 2011). Formulation containing 6.70 % SSG showed 93.52 % drug release in 4.16 hr. The in vivo studies show C_{max} 1.369 times, AUC 1.26 times more than pure drug tablet and marketed formulation. While the T_{max} is 0.83 hr, which is 3.61 times less for fast release of pioglitazone hydrochloride in comparison of pure drug tablet and marketed formulation. In contrast of that our formulation containing 4% SSG shows 99.19% drug release in 30 min. While considering these in vitro results, we are expecting to show better results in terms of bioavailability and plasma concentration in vivo. Fast disintegrating tablets (FDTs) of albendazole for its plasma exposure in to dogs containing croscarmellose sodium 5 % in FDTs (Pandit et al 2012). They found disintegration time for conventional tablet and FDTs was 12 min and 2.5 min respectively. FDTs show 70 % drug release in 30 minutes. The In vivo

study of FDTs shows C_{max} and AUC 1.53, 2.17 times respectively more than conventional tablets of albendazole. In comparison of that our formulation comprises conventional tablet without superdisintegrants and mouth dissolving tablet with 4 % croscarmellose sodium shows disintegration time 8.47 min and 58.6 sec respectively. The percent drug release for mouth dissolving tablet is 80.21 % drug released in 30 min. Upon extrapolation these results to pharmacokinetic study will definitely enhanced the peak plasma concentration greater than conventional dosage form. Based on these predictions we conclude that in vivo pharmacokinetic study is extrapolated with these results will show bioavailability 2-3 folds enhancement in which will leads to effective management of RA.

Conclusion

The method utilized for the preparation of MDTs was simple and reproducible. MDTs of flurbiprofen prepared with addition of solid dispersion technique by solvent evaporation method with PEG 6000 and superdisintegrants like sodium starch glycolate, croscarmellose sodium, kyron T-314. Formulation containing 4% kyron T-314 shows least wetting time and disintegration time, which indicates that kyron T-314 is suitable disintegrant for MDTs. The results of the study establish the flurbiprofen MDTs as a potential drug delivery system for effective pain management and long term treatment of rheumatoid arthirits with improved patient compliance. Exhaustive animal and human *in vivo* experiments are required in order to implement these findings to develop an effective treatment protocol for RA, which is going on in our laboratory.

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