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DESIGN AND DEVELOPMENT OF ACECLOFENAC FAST ISSOLVING TABLETS BY VACUUM DRYING TECHNIQUES

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Abstract

Attempts were made to prepare fast dissolving tablets of Aceclofenac by employing sublimation method to study the effect of different subliming agents and fillers. Formulations were evaluated for precompressional parameter such as angle of repose, % compressibility and Hausner's ratio. Tablets were subjected to post compressional analysis for the parameters such as hardness, friability, in-vitro disintegration time, wetting time and dissolution. Drug compatibility with excipients was checked by FT-IR studies. The results revealed that quantity of camphor; menthol; urea and type of filler significantly affect the response variables.

Key words: *Fast Dissolving Tablets, Aceclofenac, Sublimation, kyron T-114.*

Introduction

Many patients have difficulty in swallowing tablets and hard gelatin capsules and consequently do not take medications as prescribed. It is estimated that 50% of the population is affected by this problem, which results in a high incidence of noncompliance and ineffective therapy[1]. Because of the increase in the average human life span and the decline, with age, in swallowing ability, oral tablet administration to patients is a significant problem and has become the object of public attention[2, 3]. The problem can be resolved by the creation of rapidly dissolving or dispersing oral dosage forms, which do not require water to aid swallowing. The dosage forms are placed in the mouth, allowed to dissolve or disperse in the saliva, and then are swallowed in the normal way.

The fundamental principle used in the development of the fast dissolving tablets is to maximize its pore structure. Researchers have evaluated spray dried materials and plastic materials for the development of such tablets[4-5]. Vacuum drying and freeze-drying techniques have been tried by researchers to maximize the pore structure of tablet matrix. Freeze drying is cumbersome and yields a fragile and hygroscopic product [6].

Aceclofenac, (2-{2-{2(2,6-dichlorophenyl) amino phenyl} acetyl} oxyacetic acid), a non steroidal anti-inflammatory drug (NSAID) has been indicated for various painful indications[7] and proved as effective as other NSAIDs with lower indications of gastro-intestinal adverse effects and thus, resulted in a greater compliance with treatement[8].

Hence in the present work Aceclofenac fast dissolving tablets were prepared by vacuum drying technique by using different sublimating agents and to study the effect functionality differences of subliming agents on the tablet properties.

Materials And Methods

Aceclofenac was obtained as gift sample from Rantus Pharma Pvt Ltd, Hyderabad, India MCC was obtained from Maple biotech pvt ltd, Pune, India. Kyron T-114 was obtained as gift sample from Corel pharma, Ahmedabad, India. D. Mannitol, Camphor, Menthol, Urea, S.D. Lactose,

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Mannitol, Talc and Magnesium stearate were purchaged from S.D Fine chemicals ltd, Mumbai, India. All other chemicals were of analytical grade.

Methods:

Preparation of tablets:

Tablets containing 100mg of Aceclofenac were taken and then it was mixed with sprayed dried lactose, directly compressible microcrystalline cellulose, superdisintegrant and different subliming agents in different concentrations in a plastic container. Magnesium stearate and talc were passed through sieve no. 60 mixed and blended with initial mixture in the plastic container followed by compression of the blend. After compression the tablets were collected and vacuum dried at 60°C until a constant weight was obtained to ensure the complete removal of sublimable components to make the tablet porous. (Table)

Evaluation of Aceclofenac tablets:

All prepared tablets were evaluated for hardness, thickness, friability, disintegration time, wetting time and drug content. Pfizer hardness tester was used for the determination of the hardness of the tablets. The tablet was placed in contact between the plungers and the handle was pressed, the force of the fracture was recorded .The thickness of tablets were recorded during the process of compression using Calipers (Mitotoyo; Japan). The friability of the tablets was determined using a Roche Friabilator (Electrolab, EF-2 Friabilator) by taking two tablets from each batch and accurately weighed and placed in the Friabilator then operated for 100 revolutions. Then the tablets were dedusted and reweighed. Percentage friability was calculated using the formula, $F= (1-w_o/w)*100$. In the disintegration time study, the tablets were taken and introduced in each tube of disintegration apparatus, and the tablet rack of the disintegration apparatus was positioned into a 1-litre beaker containing 900ml of distilled water and time of disintegration was recorded at 37±2º c. In the wetting time study, a piece of tissue paper folded twice was placed in a petridish (with internal diameter 6.5cm) containing 5ml of distilled water. A tablet was placed on the paper and the time for complete wetting of the tablet was measured in seconds. For drug content analysis a total 10 tablets were weighed and powdered .The powder equivalent to Aceclofenac was taken and dissolved in phosphate buffer pH 7.4.After that an aliquot of the filtrate was diluted and analysed spectrophotometrically (UV 1700 Shimadzu Corporation. Japan) at 274 nm.

Invitro release studies:

The invitro dissolution study was carried out in the USP dissolution test apparatus (Electrolab TDT - 08 L Dissolution tester USP) type 2 (paddle). 900 ml of the dissolution medium (Phosphate buffer pH 7.4) was taken in vessel and the temperature was maintained at 37 ± 0.5°C. The speed of the paddle was set at 50 rpm. 5ml of the dissolution medium was withdrawn and the same amount of fresh medium was replenished to the dissolution medium. The sample withdrawn was filtered and diluted with Phosphate buffer pH 7.4 prior to analysis in the UV Spectrophotometer (UV-1700 Shimadzu Corporation, Japan) at 274 nm.

Characterization of Aceclofenac tablets:

Infrared spectroscopic study:

Fourier transformed (FTIR) spectrum of Aceclofenac, Drug with different subliming agent were obtained on a FTIR (84005 Shimadzu Japan) using the KBr disk method. Fig. No.6

Results And Discussions

The values of pre–compression parameters evaluated were within prescribed limits and indicated a good free flowing property. Results are shown in **Table**. The post compression parameters such as hardness, friability, thickness, disintegration time, wetting time, t50%, t_{90}% and drug content are shown in **Table**.

In all the formulations, the hardness test indicates good mechanical strength. Hardness of the tablets prepared by sublimation technique was increased with decrease in the amount of volatile component[9]. Friability of all formulations were less than 1%, which indicated that the tablets had a good mechanical resistance. Drug content was found to be high (≥ 98.55 %) and uniform in all the formulations. The weight variation results revealed that average percentage deviation of 20 tablets of each formula was less than ± 7.5%, which provides good uniformity. The disintegration time of tablets decreased significantly with increase in the concentration of volatile substances. Drug content of tablets ranged between 99.70 to 102.34%. The results are shown in Table. The formulations containing microcrystalline cellulose as filler (C1-M4) showed minimum disintegration time this could be attributed towards disintegrating property of microcrystalline cellulose. However, the formulations containing mannitol as filler (U1-U4) showed longer disintegration time, which could be attributed to slower dissolution characteristics of mannitol.

Tablets prepared by vacuum drying technique rapidly exhibit high pores and disintegrates the tablets rapidly. It may be due to their lowest hardness, water soluble nature of diluent and maximum porous structure was responsible for faster water uptake, hence it facilitates wicking action of cross povidone in bringing about faster disintegration, the wetting time of tablets also decrease with increase in the concentration of volatile substances. Table shows the disintegration time of the formulations were ranges between 14.30-42.30 Secs. By the addition of the superdisintegrants, the disintegration time decreased significantly ($p<0.05$). In sublimation method of preparation of tablets the disintegration time decreased regardless of the diluents used. It is because tablets prepared by sublimation method rapidly exhibits high pores and disintegrates rapidly.

Tablets prepared with 5% superdisintegrants and 20% camphor showed least disintegration time as compared to all other formulations this is because of their porous structure responsible for faster uptake hence it facilitates wicking action of crosspovidone in bringing about faster disintegration. The dissolution profile of tablets is shown in Fig. The dissolution of the drug from the tablets prepared by vacuum drying technique using camphor had was quicker than those prepared by other subliming agents. This may be due to their porous structure, which is responsible for faster disintegration. Cross providence containing tablets rapidly exhibits high capillary activity and pronounced hydration with a little tendency to gel formation and disintegrate the tablets rapidly[13].

In-vitro dissolution studies of all formulations were carried out in phosphate buffer pH 7.4, this data reveals that overall, the formulation C4, M4, and U4 shows nearly faster drug release. The formulations C4, M4 and U4, 50% of drug released in 2.55 min, 4.32 min, and 712 min respectively, and 90 % of drug released in 6.12min, 10.24 min, and 15.76 min respectively when compared to other formulations. C4 promising fast dissolving tablet containing 20 % camphor as subliming agent, M4 promising fast dissolving tablet containing 20 % menthol as subliming agent, U4 fast dissolving tablet containing 20 % urea as subliming agent. Dissolution of drug from tablets containing highest volatile substance and MCC as filler (C4 and M4) were quicker than other formulations. It may be due to highest porosity, lowest hardness and disintegrating property of MCC, which leads to faster water uptake hence it facilitates wicking action of crospovidone in bringing about faster disintegration and dissolution. Dissolution profiles of best formulations prepared by using different subliming agents were shown in **Fig.**

Infrared spectroscopic study:

The prominent IR absorption peaks of Aceclofenac showed at 3319 and 3267 these broad peaks may be due to OH hydrogen bonding.2970 is NH aromatic stretching, peaks near 2937 including 1921 may be due to CH stretching of CH_2 groups, carbonyl group vibration at 1770 and 1716. Peaks at1589, 1577 and 1508 indicates the presence of C=C ring stretching. All these principal IR peaks of Aceclofenac were present in all formulations. This clearly indicates that there is no interaction between drug and carrier.

Conclusion

The results of disintegration, time, wetting time and dissolution rate revealed that the amount of volatile component and type of filler significantly affect the dependent variables likes disintegration time, wetting time and dissolution rates. Thus it is concluded that fast disintegrating tablets can be prepared with a view of obtaining faster action of the drug and would be advantageous in compilations to the currently available conventional dosage forms. With the adopted vacuum drying technique an optimum point can be reached in the shortest time with minimum efforts and this technique would be an effective alternative approach compared with the use of more expensive adjuvant in the formulation of fast disintegrating tablets. Finally it can be concluded that the superdisintegrant and volatile substances had played an important role to decrease disintegration time and to enhance the dissolution rate in vacuum drying technique, hence could be used to prepare the Fast Dissolving Tablets.

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Table 1: Composition of fast disintegrating tablets

Ingredients (mg)	C1	C2	C3	M1	M2	M3	U1	U2	U3
ACECLOFENAC	100	100	100	100	100	100	100	100	100
Spray dried Lactose	109	94	79	109	94	79	109	94	79
MCC	30	30	30	30	30	30	-	-	-
Mannitol	-	-	-	-	-	-	30	30	30
Crospovidone	15	15	15	15	15	15	15	15	15
Camphor	30	45	60	-	-	-	-	-	-
Menthol	-	-	-	30	45	60	-	-	-
Urea	-	-	-	-	-	-	30	45	60
Kyron T-114	10	10	10	10	10	10	10	10	10
Magnesium stearate	3	3	3	3	3	3	3	3	3
Talc	3	3	3	3	3	3	3	3	3
Total weight	300	300	300	300	300	300	300	300	300

Table 2: Tablet weight before vacuum drying (BVD) and after vacuum drying (AVD)

Formulation	Tablet Weight	
	BVD	AVD
C1	301(0.68)	269 (0.75)
C2	300 (0.55)	270 (1.34)
C3	302 (0.67)	269(1.30)
M1	301 (0.70)	255 (1.50)
M2	299(1.00)	254 (2.30)
M3	302(0.95)	253 (1.70)
U1	302 (0.34)	238 (1.45)
U2	301 (0.76)	239(0.10)

U3	300 (1.55)	238(0.75)

Table: Pre-Compressional parameters.

Formulation	Parameters		
	Angle of repose (θ) (± SD), n=3	**Compressibility (%) (± SD), n=3**	**Housners ratio (%) (± SD), n=3**
C1	22.55 (0.72)	24.22 (0.22)	1.21 (0.04)
C2	23.46 (1.52)	15.32 (0.92)	1.35 (0.07)
C3	24.59 (1.37)	14.35 (0.12)	1.34 (0.04)
M1	20.37 (0.90)	15.00 (2.10)	1.12 (0.02)
M2	25.22 (1.22)	13.22 (1.10)	1.32 (0.04)
M3	23.24 (1.19)	14.32 (0.58)	1.25 (0.05)
U1	25.24(0.46)	13.55 (1.55)	1.36 (0.04)
U2	25.35 (0.75)	13.57 (1.22)	1.22 (0.07)
U3	23.62 (2.10)	14.33 (1.00)	1.25 (0.06)

Table: Post compression parameters of tablets

Parameters	Formulations								
	C1	**C2**	**C3**	**M1**	**M2**	**M3**	**U1**	**U2**	**U3**
Hardness (kg/cm^2) ± SD, n=3	4.25 ± 0.15	4.20 ±0.12	4.00 ±0.10	3.90 ±0.07	3.40 ± 0.50	3.44 ± .22	4.00 ± 0.50	4.25± 0.15	4.55 ± 0.35
Friability (% w/w) ± SD, n=3	0.34 ± 0.08	0.35 ± 0.04	0.37 ±0.12	0.38 ± 0.22	0.56 ± 0.08	0.55 ±0.10	0.45 ± 0.12	0.30 ± 0.33	0.22 ± 0.06
Thickness (mm) ± SD, n=6	3.65 ± 0.05	3.25 ±0.07	3.50 ±0.02	3.75 0.09	3.34 ±0.01	3.33 ±0.02	3.62 ±0.03	3.68 ±0.03	3.70 ±0.07
Weight variation ± SD, n=10	300 ± 1.55	299 ±1.30	301 ±1.22	298 ± 1.20	300 ± 1.20	298 ± 1.50	300 ± 1.25	302 ± 1.60	301 ± 0.35
Wetting time (Sec) ± SD, n=6	35 ± 0.22	30 ± 0.06	19 ± 0.31	40 ± 0.29	37 ± 0.34	26 ± 0.23	58 ± 0.56	45 ± 0.24	31 ± 0.44
Water absorption ratio (%) ± SD, n=6	80.50 ± 0.19	81.27 ± 0.22	80.45 ±0.18	81.46 ± 0.24	82.00 ± 0.17	85.00 ± 0.21	88.50 ± 0.31	89.26 ± 0.44	88.72± 0.37
***In-vitro* disintegration time (Sec) ± SD, n=6**	25.30 ± 0.06	27.50 ± 0.08	14.30 ±0.09	32.30 ± 0.09	28.30 ± 0.09	20.02 ± 0.08	42.30 ± 0.06	39.00 ± 0.05	28.00 ± 0.09
Drug content (%) ± SD, n=6	101.00 ± 1.23	102.00 ± 1.25	99.98 ±1.67	100.50 ± 1.87	99.70 ± 2.00	102.00 ±0.12	101.00 ±1.00	102.34 ± 0.57	100.42 ± 1.33

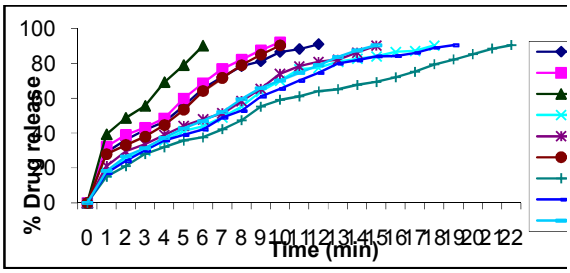

FIG: Dissolution profiles of all formulations.

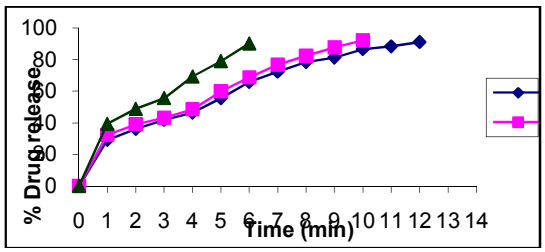

FIG: Dissolution profiles of formulations prepared by using Camphor as subliming agent.

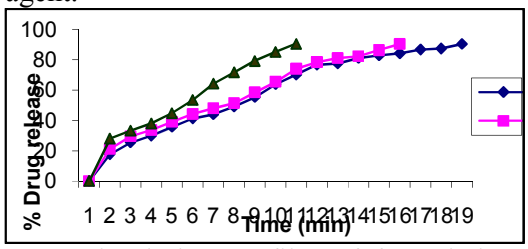

FIG: Dissolution profiles of formulations prepared by using Mannitol as subliming agent.

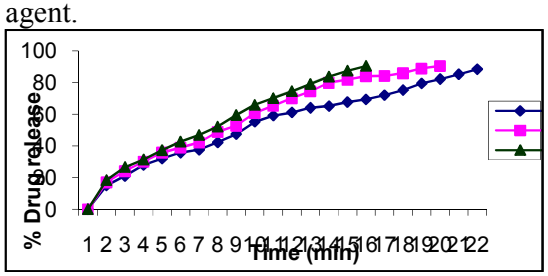

FIG :Dissolution profiles of formulations prepared by using Urea as subliming agent.

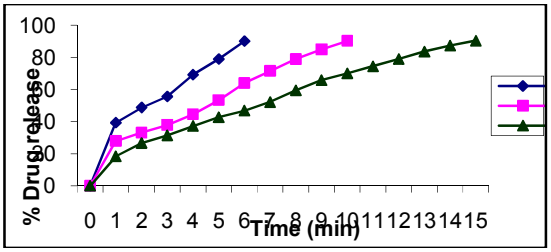

FIG: Dissolution profiles of best formulations prepared by using different subliming agents.

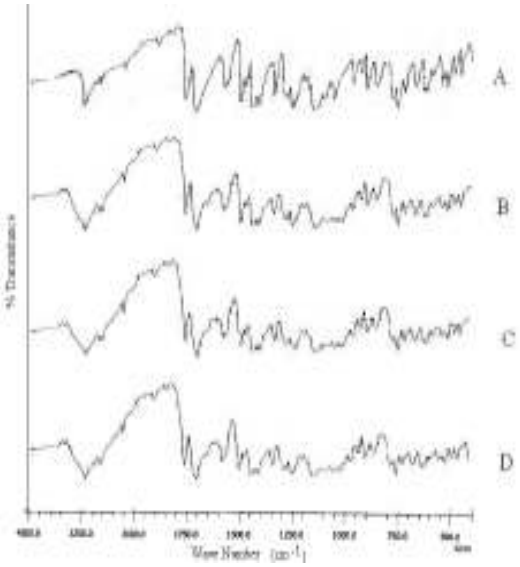

FIG: FTIR spectrum of Aceclofenac pure drug (A), Drug with Camphor (B), Drug with Menthol (C), Drug with Urea (D).