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STUDIES ON APPLICATION OF PROSOLVE AS A DIRECT COMPRESSIBLE VEHICLE FOR IMPROVING THE DISSOLUTION RATE OF POORLY SOLUBLE DRUGS

RAMANJI REDDY T.[1], RAVI P.[1], KRISHNA B.V.R.[2], PADMAVATHI D.[3] AND AJAY BABU CH.[4]

For author affiliations, see end of text

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ABSTRACT

Prosolve, a new directly compressible vehicle consists of microcrystalline cellulose (98%) and colloidal silicon dioxide (2%). Piroxicam (20 mg) tablets, celecoxib (100 mg) tablets and aceclofenac (100 mg) tablets were formulated employing prosolve and three super disintegrants namely pregelatinised starch, sodium starch glycolate and croscarmellose sodium by direct compression method with a view to enhance their dissolution rate. In the micromeritic evaluation microcrystalline cellulose and its blends with other tablet ingredients exhibited excellent to good flow needed for direct compression. All the tablets formulated employing prosolve fulfilled the Pharmacopoeial standards with regard to various tablet characters. These tablets also gave 2 to 5 fold increase in the dissolution rate when compared to commercial tablets. Among the three disintegrants sodium starch glycolate gave higher dissolution rates when compared with both pregelatinised starch and croscarmellose sodium.

Keywords: Prosolve, Piroxicam, Celecoxib, Aceclofenac and Direct compression method**.**

INTRODUCTION

Great interest in direct compression as a method of manufacture of tablets has been evident in recent years and this has resulted in a wide range of direct compression tablet formulations being introduced. Several directly compressible vehicles with good free flow and compaction properties have been developed in recent years. Prosolve is one such recently developed directly compressible vehicle. Prosolve, also known as silicified microcrystalline cellulose consists of microcrystalline cellulose (98%) and colloidal silicon dioxide (2%). Prosolve has improved compaction properties in both wet granulation and direct compression methods compared to conventional microcrystalline cellulose [1, 2]. The objective of the present study is to formulate and evaluate piroxicam and aceclofenac tablets employing Prosolve by direct compression method for enhancing their dissolution rates. Piroxicam, celecoxib and aceclofenac are widely prescribed non-steroidal anti inflammatory and analgesic drugs. They are practically insoluble in water and aqueous fluids. The poor aqueous solubility of these drugs gives rise to difficulty in the formulation of solid dosage forms such as tablets, leads to low and variable dissolution rate and bioavailability. Direct compression method employing prosolve was tried to enhance the dissolution rate of piroxicam, celecoxib and aceclofenac.

Mintong Guo et al (2003) investigated the SMCC's performance to that of other excipients commonly used in hard gelatin capsule direct-fill formulations. All capsules were filled using a fully instrumented Zanasi LZ-64 automatic capsule-filling machine. Four grades of SMCC [SMCC 50, SMCC 90, SMCC HD90, and an experimental-grade (SMCC X)] were studied. Anhydrous lactose (direct tableting grade), pregelatinized starch (PGS) (Starch 1500), and microcrystalline cellulose (MCC) (Emcocel 90M) were chosen as the control fillers. Capsules were evaluated for capsule fill weight, relative standard deviation of capsule fill weight, plug ejection force, plug maximum breaking force (MBF), and the dissolution of two marker compounds (acetaminophen and piroxicam). Formulations containing 5% piroxicam, 30% acetaminophen, or 50% acetaminophen exhibited faster drug dissolution when MCC or SMCC was the filler than when anhydrous lactose or PGS was the filler. The data suggest that SMCC could be a suitable direct-fill excipient for hard shell capsule formulations [3]

Ahmad Aljaberi *et al* (2009) studied the silicified microcrystalline cellulose (SMCC), microcrystalline cellulose (MCC), and physical mixture of MCC–colloidal silicon dioxide (MCC/CSD at 98:2 ratio) as extra granular compression aids to address the processing and dissolution stability issues of this formulation. The compactibility and stickiness upon compression over extended period of time as well as the dissolution of R411 formulations incorporating the aforementioned compression aids were investigated. In addition, the water sorption/desorption properties of these compression aids were determined. The formulations containing SMCC provided superior dissolution stability over the other compression aids evaluated in the study. Novel functionalities of SMCC are presented in terms of sticking prevention while having the most beneficial effect on dissolution stability in R411 formulation [4].

Piroxicam (20 mg), celecoxib (100mg) and aceclofenac (100 mg) tablets were formulated employing prosolve and three disintegrants namely pregelatinised starch, sodium starch glycolate and croscarmellose sodium by direct compression method with a view to enhance their dissolution rate.

Materials

Piroxicam, celecoxib and aceclofenac were gift samples from M/s. Aristo Pharmaceuticals Ltd., Mumbai. Prosolve was a gift sample from M/s. Orchid Health Care Ltd., Chennai. Pregelatinised starch, sodium starch glycolate and croscarmellose sodium were procured from commercial sources. All other materials used were of pharmacopoeial grade.

Methods

Preparation of tablets

Piroxicam (20 mg), celecoxib (100mg) and aceclofenac (100 mg) tablets were prepared employing prosolve by direct compression method as per the formulae given in Table 1. All the ingredients were blended thoroughly in a closed HDPE bottle and were directly compressed into tablets to a hardness of 6-8 kg/cm^2 on a 16-station Cadmach tablet machine using 9 mm round and flat punches. All the tablets prepared were evaluated for drug content, hardness, friability, and disintegration time and dissolution rate. Hardness of the tablets was tested by using a Monsanto Hardness Tester. Friability of the tablets was determined in a Roche Friabilator. Disintegration time was determined in a Thermonic tablet Disintegration Test machine using water as test fluid.

Estimation of drug content

Drug content of the prepared tablets was estimated by UV Spectrophotometric method based on the measurement of absorbance at 333 nm in the case of Piroxicam tablets, 254 nm in the case of celecoxib and at 275 nm in the case of aceclofenac tablets. The methods were validated for linearity, precision and accuracy. The methods obeyed Beer's law in the concentration range 1-10 μg/ml. The accuracy and precision of the methods were in the range of 0.4 - 0.8 %. No interference from the excipients used was observed [6-7].

Dissolution rate study

Dissolution rate of drug from the prepared and commercial tablets was studied using 8 - station Dissolution Rate Test Apparatus (LABINDIA, DISSO 2000) employing a paddle stirrer at 50 rpm and 37 ± 0.5^0C. Hydrochloric acid (0.1 N), water containing 1% sodium lauryl sulphate and phosphate buffer of pH 7.4 were used as dissolution fluid (900 ml) respectively for piroxicam, celecoxib and aceclofenac tablets. Samples of 5 ml each were withdrawn at 5, 10, 20, 30, 40, 50 and 60 minutes and assayed at 333 nm in the case of piroxicam, 254 nm in the case of celecoxib and 275 nm in the case of aceclofenac using Shimadzu UV-150 double beam UV-spectrophotometer. Each sample with drawn was replaced with an equal amount of fresh dissolution medium. For comparison, dissolution rate of commercial tablets in each case was also studied. Dissolution rate experiments were conducted in triplicate [5].

Dissolution data analysis

Dissolution data were analyzed as per zero and first order kinetic models. Dissolution efficiency (DE_{30}) values were calculated as described by Khan[6] and T_{50} (time for 50% dissolution) values were recorded from the percent dissolved vs. time plots and the data is appended in Table 2.

Micromeritic evaluation

The flow characteristics of tablet granulations (i.e. blend of powders before compression) were assessed in each case by measuring the angle of repose by fixed funnel method and Carr's compressibility index by standard tapping method [8]. The data is given in Table 3.

TABLE 1

FORMULAE OF TABLETS PREPARED EMPLOYING PROSOLVE

Ingredient (mg/tablet)	Formulations								
	F1	F2	F3	F4	F5	F6	F7	F8	F9
Piroxicam	20	20	20	-	-	-	-	-	-
Celecoxib	-	-	-	100	100	100	-	-	-
Aceclofenac	-	-	-	-	-	-	100	100	100
Pg. starch	30	-	-	30	-	-	30	-	-
SSG	-	10	-	-	10	-	-	10	-
Croscarmellose sodium	-	-	10	-	-	10	-	-	10
Lactose	-	20	20	-	-	-	-	-	-
Prosolve	142	142	142	100	120	120	100	120	120
Talc	4	4	4	4	4	4	4	4	4
Magnesium stearate	4	4	4	4	4	4	4	4	4
Total Weight of Tablet (mg)	200	200	200	238	238	238	238	238	238

TABLE 2

DISSOLUTION PARAMETERS OF TABLETS FORMULATED EMPLOYING PROSOLVE

Formulation	D.T. (sec.)	T_{50} (min)	DE_{30} (%)	K_1 (min^{-1})
F1	10	8.5	61.52	0.0506
F2	7	4.5	68.03	0.0640
F3	6	4.0	70.52	0.0518
Piroxicam Commercial	19	12	50.30	0.0308
F4	14	21	41.15	0.0139
F5	11	20	43.34	0.0145
F6	10	36.5	37.77	0.0103
Celecoxib commercial	72	>60	11.53	0.0051
F7	18	4.5	60.90	0.0616
F8	14	4.5	57.62	0.0827
F9	14	4.0	65.23	0.0782
Aceclofenac commercial	21	8.0	53.38	0.0164

TABLE 3

MICROMERITIC PROPERTIES OF PROSOLVE AND ITS TABLET GRANULATIONS

Formulation	Angle of Repose (^{0})	Compressibility Index (%)
Prosolve	18.34	15.8
F1	24.04	9.1
F2	19.98	14.9
F3	23.96	20.0
F4	17.74	18.0
F5	21.80	20.30
F6	22.92	22.30
F7	24.24	20.0
F8	21.24	17.5
F9	20.55	16.7

RESULTS AND DISCUSSION

Piroxicam (20 mg), celecoxib (100 mg) and aceclofenac (100 mg) tablets were formulated employing prosolve, a new directly compressible vehicle by direct compression method. Angle of repose and compressibility index of prosolve as such and tablet granulations before compression were measured to assess their suitability for direct compression. The results of micromeritic evaluation are given in Table 3. Angle of repose less than 25^0 indicates excellent flow. Carr's compressibility index value in the range 5–15% indicates excellent flow and in the range 16–21% indicates fair to good flow. Angle of repose value of all the products tested were < 25^0 indicating excellent flow of prosolve and all the tablet granulations tested. Whereas compressibility index values of the products tested were in the range 9–21 % indicating fair to good flow. As prosolve and the tablet granulations (the blend of prosolve and other ingredients) exhibited excellent to good flow characteristics, they are considered suitable for direct compression method.

The hardness of the tablets prepared was in the range of 6 – 8 kg/cm^2 Weight loss in the friability test was less than 1.0 % in all the cases. The tablets contained drug within 100±3 % of the labeled claim. All the formulated tablets of piroxicam, celecoxib and aceclofenac disintegrated within 18 seconds. As such all the tablets formulated employing prosolve are of good quality fulfilling the official (I.P) requirements with regard to drug content, hardness, friability and disintegration time.Dissolution parameters of the formulated tablets are summarized in Table 2. All the tablets formulated employing prosolve gave rapid and higher dissolution than the commercial products with all three drugs. Drug dissolution from the tablets followed first order kinetics. A 2 to 5 fold increase in the dissolution rate (K_1) was observed with formulated tablets when compared to commercial tablets. Three disintegrants namely pregelatinised starch, sodium starch glycolate and croscarmellose sodium were used in each case. With all the three drugs tablets formulated employing sodium starch glycolate gave higher dissolution rates and DE_{30} values than those formulated with pregelatinised starch and croscarmellose sodium. The compared $DE_{30\%}$ values with commercial products can be seen in figure 1, figure 2 and figure 3 respectively. The order of performance of disintegrants in enhancing the dissolution rate was sodium starch glycolate > croscarmellose sodium > pregelatinised starch in the case of piroxicam and aceclofenac and sodium starch glycolate > pregelatinised starch > croscarmellose sodium in the case of celecoxib.

Figure 1:

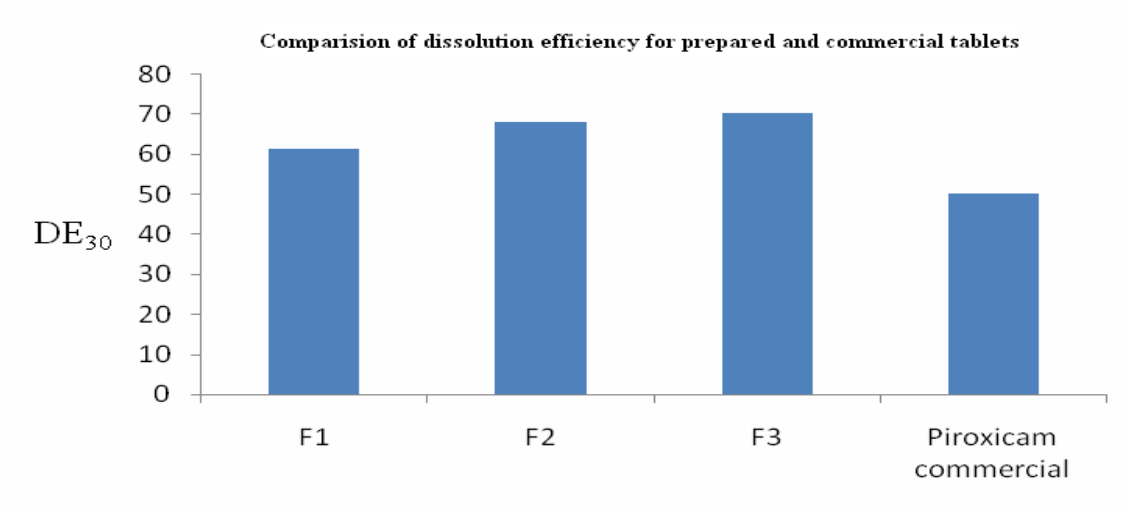


Figure 2:

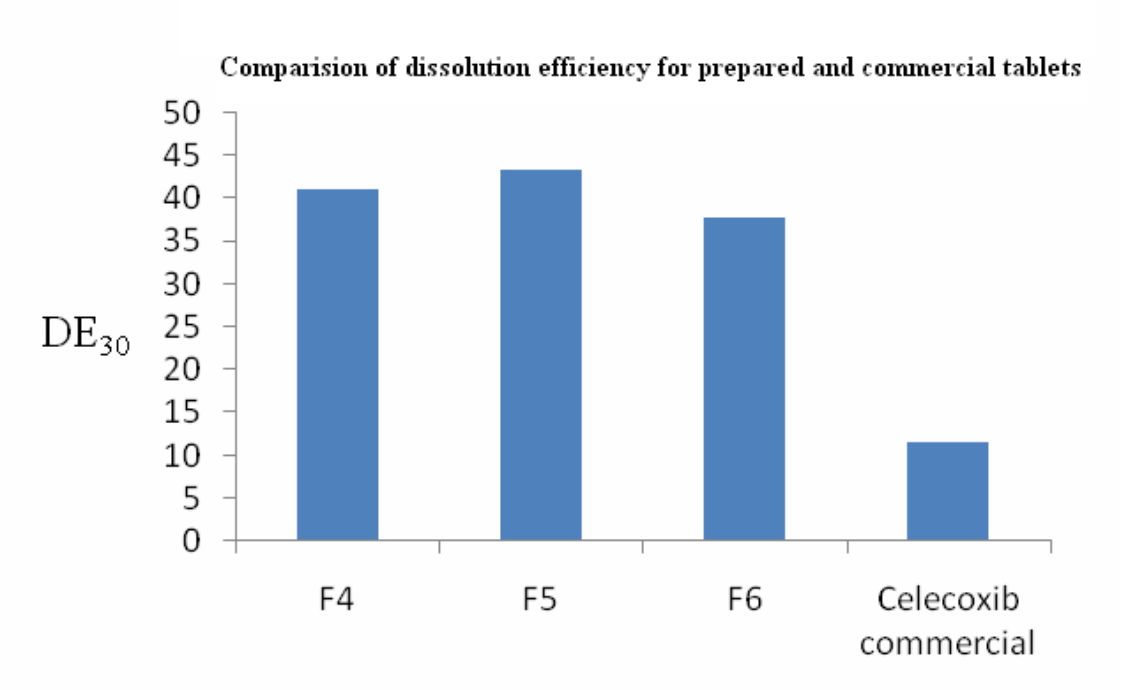
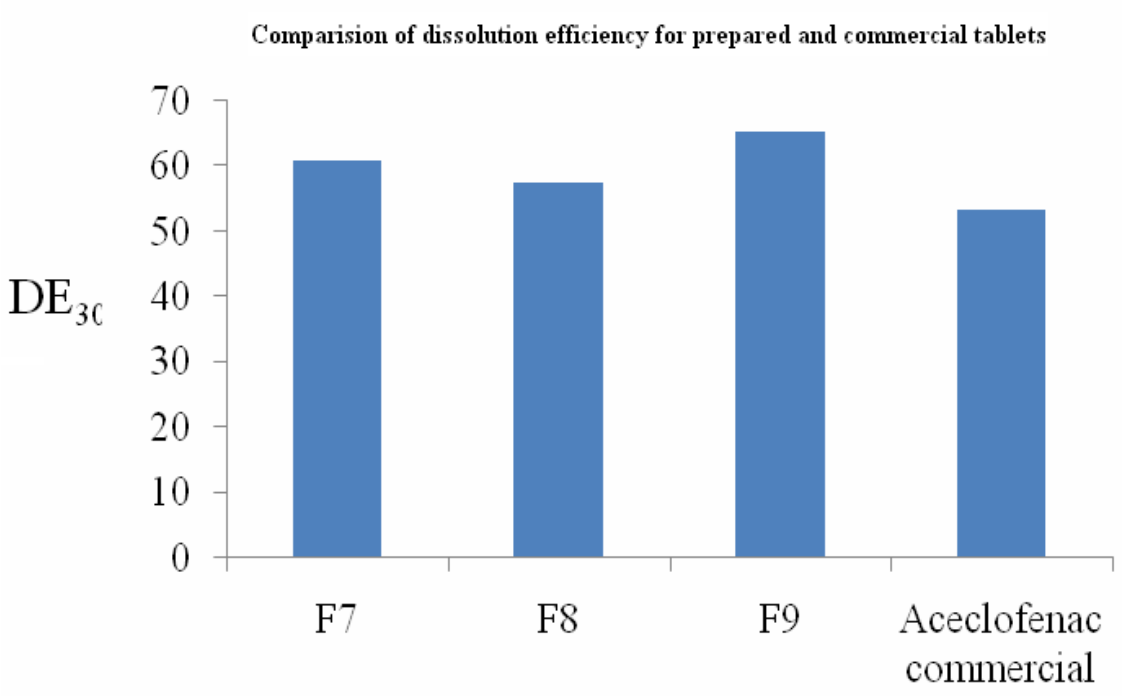


Figure 3:



CONCLUSION

Prosolve, a new directly compressible vehicle and other tablet ingredients exhibited excellent to good flow needed for direct compression. Tablets formulated employing prosolve gave 2 to 5 fold increase in the dissolution rate with piroxicam, celecoxib and aceclofenac when compared with commercial tablets. Thus, prosolve could be used as directly compressible vehicle to prepare piroxicam, celecoxib and aceclofenac tablets and the tablets employing prosolve gave higher dissolution rates and DE_{30} values than the commercial brands in each case.

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AUTHOR AFFILIATIONS:

1. Sarada College of Pharmaceutical Sciences, Narasaraopeta, A.P, India.

2. Dr.Reddy's Laboratories Ltd., Hyderabad, A.P, India.

3. P. Rami Reddy Memorial College of Pharmacy, Kadapa, A.P, India.

4. A.U College of Pharmaceutical Sciences, AU, Visakhapatnam, A.P, India

ADDRESS FOR COMMUNICATION:

T. Ramanjireddy
Sarada College of Pharmaceutical sciences, Narasaraopeta-522602
Andhra Pradesh, India.
Email: rmnjrddy@gmail.com
Phone No.: +91-9618479909