DEVELOPMENT AND EVALUATION OF FAST DISSOLVING TABLET USING COPROCESSING TECHNIQUE FOR PEDRIATRIC PATIENTS

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Abstract: 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 improvement as well as masking the undesirable properties of individual. Co-processed excipients are prepared by incorporating one excipient into the particle structure of other excipients using processes such as co-drying. Coprocessing excipient leads to the formation of excipients granulates with superior properties compared with physical mixtures of components or individual components. Usually a combination of plastic and brittle materials is used for co-processing. This combination prevents storage of too much elastic energy during the compression, which results in a small amount of stress relaxation and a reduced tendency of capping and lamination thereby optimum tableting performance. The proposed study is prepared and characterizes the fast dissolving tablet containing monteleukast co-processed particles (MCPs) formulation with using natural superdisintegrant with direct compression. The superdisintegrants and its concentration shall be during the preparation of Monteleukast Fast Dissolving Tablets (MFDTs) with monteleukast by using direct compression via employing different excipients in different ratio including: superdisintegrants {sodium starch glycolate (SSG), Ac-Di-Sol, crosspovidone (CP), Spray dried lactose which were used alone and in various combination and mannitol, along with lubricant and glidants. The prepared MFDTs with a short disintegration time, sufficient mechanical strength, better patient compliance, and acceptable stability profile by employing different methods of preparation and studying different variables affecting pre and post-compression parameters. The results of the release kinetics study showed that all the formulations obeyed first order drug release profile more closely, i.e., the release rate depended upon the initial concentration of drug.

Keywords: Coprocessing excipients, monteleukast, superdisintegrants, Fast Dissolving

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Introduction: Oral tablet administration to patients is a significant problem and has become the object of public attention. The problem can be resolved by the creation of rapidly dispersing or dissolving oral forms, which do not require water to aid swallowing. A much broader platform for the manipulation of excipient functionality is provided by co-processing or particle engineering two or more excipients. 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 improvement as well as masking the undesirable properties of individual [1]. Co-processed excipients are prepared by incorporating one excipient into the particle structure of other excipients using processes such as co-drying. A similar principle was applied in developing silicified microcrystalline cellulose which is the most widely used co-processed excipient. Coprocessing excipient leads to the formation of excipients granulates with superior properties compared with physical mixtures of components or individual components [2]. Hence, co-processing these two kinds of materials produces a synergistic effect in terms of compressibility by selectively overcoming the disadvantages and can help improve functionalities such as compaction performance, flow properties, strain rate sensitivities, lubricant sensitivity or sensitivity to moisture. Because of their high aqueous solubility and sweetness, which imparts a pleasing mouth feel and good taste masking, nearly all formulations for rapidly dissolving tablets contain sugar based materials [3]. The Fast dissolving tablets are synonymous with mouth fast disintegrating tablets, melt in mouth tablets, rapimelts, porous tablets, orodispersible, quick dissolving or rapidly disintegrating tablets. Their growing importance was underlined recently when European pharmacopoeia adopted the term “Fast dissolving tablet” as a tablet that can be placed in the mouth where it disperses rapidly, before swallowing. Direct compression is defined as the process by which tablets are compressed directly from powder blends of the active ingredients and suitable excipients including fillers disintegrating agents and lubricants, which flow uniformly into a die cavity and form into a firm compact [5]. The main advantages of the direct compression method is that it is cost-effective when compared to all other methods ,uses conventional equipment and commonly available excipients, limited number of processing steps and higher doses can be easily accommodated [6]. The orally disintegrating property of the tablet is

attributable to a quick ingress of water into the tablet matrix resulting in its rapid disintegration. Hence, the basic approaches to developing orally disintegrating tablets include maximizing the porous structure of the tablet matrix, incorporating the appropriate disintegrating agent, and using highly water-soluble excipients in the formulation [7]. FDT technology is relatively new to the industry and had a significant impact on patients of all ages and taste masking being an essential requirement for FDTs for commercial success. Taste-masking of bitter or with objectionable-tasting drug substances is critical for any orally-administered dosage form. Less commonly, active pharmaceutical ingredients to be incorporated are tasteless and do not require taste masking. Taste masking of bitter drugs become necessity in case of oral administration and selection of technology depends upon the bitterness of drugs and their compatibility with taste masking agents that does not affect the bioavailability of drug [8]. The taste masking involves various physical and chemical method that prevent the interaction of taste bud with drugs, Two approaches are commonly utilized to overcome bad taste of the drug. The first includes reduction of drug solubility in saliva, where a balance between reduced solubility and bioavailability must be achieved. Another approach is to alter the ability of the drug to interact with taste receptor Popular approaches in the development of taste masking in liquid dosage form include use of flavor followed by viscosity modification and if failed, by ion exchange resin [9]. Montelukast is a leukotriene receptor antagonist used as part of an asthma therapy regimen, to prevent exercise induced bronchoconstriction, and to treat seasonal allergic rhinitis. Montelukast is a leukotriene receptor antagonist that demonstrates a marked affinity and selectivity to the cysteinyl leukotriene receptor type-1 in preference to many other crucial airway receptors like the prostanoid, cholinergic, or beta-adrenergic receptors. As a consequence, the agent can elicit substantial blockage of LTD4 leukotriene-mediated bronchoconstriction with doses as low as 5 mg. The proposed work develop the solid dosage forms with using co-processing based novel concept of two or more excipients interacting at the sub particle level. Co-processed excipients are prepared by incorporating one excipient into the particle structure of other excipients using processes such as co-drying. A similar principle was applied in developing silicified microcrystalline cellulose which is the most widely used co-processed excipients natural superdisintegrants and its concentration for the preparation of FDTs. Superdisintegrants are primarily required for fast dissolving tablets for this purpose with novel

coprocessing techniques. Coprocessing excipients leads to the formation of excipients granulates with superior properties compared with physical mixtures of components or individual components. Usually a combination of plastic and brittle materials is used for co-processing [10]. The objective of proposed work is to provide a synergy of functionality improvement as well as masking the undesirable properties of individual. The excipients as mannitol and microcrystalline cellulose are superior to physical mixtures of mannitol and microcrystalline cellulose used in fast dissolving tablets.

Material and Method

Preparation of co-processed particles in various proportions of mannitol and microcrystalline cellulose: The excipients mixture was prepared by spray drying process of various proportions of mannitol and microcrystalline cellulose to have ratios of 1:1, 2:1, 3:1. The required proportions of powdered mannitol and microcrystalline cellulose, which were previously passed through sieve no. 80 were dispersed in absolute alcohol to have the final solid content of feed suspension of 10%w/w. Then, suspensions were mixed thoroughly using a magnetic stirrer for 10 min to obtain homogeneous feed dispersion. The dispersions were spray dried with a JISL mini lab spray drier to prepare the co-processed excipients. The process parameters were set as follows; inlet temperature (120º); outlet temperature (60º); aspirator setting (12-18); pump setting (10 ml/min); air pressure 2 kg/cm2.

Evaluation of monteleukast co-processed particles (MCP1 – MCP3)

Physical appearance: All the batches of monteleukast co-processed particles were evaluated for color and appearance.

Solubility studies: The solubility of drug was determined in distilled water, 0.1N HCI, ASA pH 6.8 and phosphate buffer pH 7.4. A accurate weighed 25 mg drug was kept in conical flask and required quantity upto 50 ml were kept in burrete. Now start the addition of 5 drops to conical flask containing drug. The conical flask regularly shaking and the amount of dissolution media noted, at which the drug was solubilized and kept for shaking at 37ºC for 24 h in orbital shaking machine. Aliquots were filtered through whatman filter paper and the solubility of drug was calculated with unit mg/ ml.

Differential Scanning Calorimetry (DSC): Pure drug (Monteleukast (ML), co-processed particles (5-10 mg) was heated in hermetically sealed aluminium pans with a heating rate of

10°C/min under nitrogen atmosphere (flow rate 20 ml/min) and thermograph were recorded using differential scanning calorimeter (Perkin-Elmer DSC7, USA).

SEM studies: The co-processed particles were evaluated for their physical structural changes in the surface topography of the drug particles by scanning electron microscopy (SEM) technique.

Percent yield: Percent practical yield was calculated to know about percent yield or efficiency of the any method thus it helps in selection of appropriate method of production. The co-processed particles were collected and weighed to determine practical yield (PY) from the following equation:

$$\text{Percent practical yield \%} = \frac{\text{Practical mass}}{\text{Theoretical mass (drug + carrier)}} * 100$$

Preparation of fast dissolving tablets: Monteleukast Fast Dissolving Tablets (formulas MFDTs1- MFDTs3) were prepared by direct compression method according to the formulas given in **(Table 6.3)**. The content of optimized effective formulation was MCP2, which containing Mannitol : HPMC (2:1) co-processed particles ratio. The equivalent amount of drug 25 mg presents in co-processed particles MCP2 about 200 mg total weight powder. The procedure is as follows: All the ingredients (except lubricants and glidant) were passed through sieve mesh #40 meshes separately. Then weighed and mixed in geometrical order for about 10 min. Then lubricants and glidant were added to the mixture and mixed for about 2 min. Finally an accurate weight of the blend was compressed into tablets of 370 mg using 8 mm punch tablet compressing machine.

Evaluation of fast dissolving tablets: The prepared **MFDTs** were evaluated for thickness of tablets, uniformity of weight, hardness, friability, disintegration time, water uptake percent, swelling studies, rupture test, drug content, in-vitro drug release study.

Flow properties of powders: The flow properties of powder were characterized for identification of flow character of powder in terms of carr's index, hausner's ratio and angle of repose.

Thickness and diameter: Ten tablets from each formulation were taken randomly and their thickness was measured with a digital vernier caliper**.**

Weight variation: Twenty tablets were selected randomly from each formulation and weighed individually. The individual weights were compared with the average weight for the weight variation.

Hardness: The test is done using hardness tester (Erweka TBH 320) and the hardness was expressed in kg/cm^2 as a force required crushing the tablets. The mean of six determinations was used ± SD 10.

Friability: Twenty tablets were weighed and placed in a Roche friabilator and the equipment was rotated at 25 rpm for 4 min. The tablets were taken out, dedusted and reweighed. The percentage friability of the tablets was calculated using equation:

$$\% \text{ Friability} = \frac{\text{Initial weight} - \text{Final weight}}{\text{Initial weight}} \times 100$$

Drug Content Uniformity: One tablet of the all formulation was placed in 100 ml volumetric flask, 50 ml of ASS (pH 6.8) was added, shaked by mechanical means for 30 min., ASS (pH 6.8) added to volume, filtered, diluted suitably, and finally the quantity of monteleukast in the tablet was measured spectrophotometrically at λmax of 234 nm.

in vitro Disintegration Test: The artificial saliva solution (ASS) was prepared of 0.426 g disodium hydrogen orthophosohate, 1.680 g Sodium bicarbonate, 0.147 g calcium chloride, 1N hydrochloric acid to adjust pH to 6.8, and distilled water up to 1L. The in vitro disintegration test was done for all formulation at 37°C using artificial saliva solution (ASS) as a dissolution medium for the test. Disintegration apparatus with a basket rack assembly containing six open ended tubes and 10-mesh screen on the bottom was used. A tablet was placed in each tube of the basket and the time required for complete disintegration of the tablets with no palpable mass remaining in the apparatus was measured.

Wetting time and Water absorption ratio: The evaluation of such parameters, the method was slightly modified by using artificial saliva solution as a medium. A piece of tissue paper folded twice was placed in a small Petri-dish (internal diameter = 6.5 cm) containing 10 ml of ASS and 0.05% w/v amaranth solution (coloring agent). A tablet was placed on the tissue paper and the time required for complete wetting of the tablets was recorded as wetting time.

The mean of three determinations was used ± SD 13. The same procedure of wetting time test was followed for determining the water absorption ratio (WAR) and it was determined according to the equation:

$$WAR = [(Wa – Wb) / Wb] \times 100$$

where, Wb and Wa were the weights of the tablets before and after the test.

in vitro Dispersion Time: Dispersion time is very important for Monteleukast Orally Disintegrating Tablets which are desired to be less than one minute for orally dispersible tablets. This rapid disintegration assists swallowing and also plays a role in drug absorption in buccal cavity, thus promoting bioavailability. In vitro dispersion time was measured by dropping a tablet in a small beaker containing 6ml of ASS (pH 6.8) and agitated mildly. The time required for complete dispersion of tablets as fine particles was noted as dispersion time.

in vitro Dissolution Studies: In vitro dissolution studies were performed for the formulation containing monteleukast (25mg) by using type I (Basket) dissolution apparatus at 100 rpm, and 900 ml of ASS (pH 6.8) was used as a dissolution medium. Temperature of dissolution medium was maintained at 37±0.5°C. Five ml aliquot of the dissolution medium was withdrawn at specific time intervals and replaced by fresh ASS (pH 6.8) solution. The aliquot was filtered and diluted suitably and then analyzed by using UV spectrophotometrically at the λmax of 232 nm. To analyze the in vitro release data, various kinetic models including (zero order, first order, Higuchi and Korsmeyer-Peppas model) were used to describe the release kinetics.

Result and Discussion: The physical appearance and color of prepared co-processed particles was granular product in appearance and off-white in color. The solubility studies were conducted in different media for all the prepared co-processed particles and compared with pure drug. From the solubility studies, it was found that as the increase in pH of the media increased the solubility i.e. MCPs showed greater solubility in ASS phosphate buffer pH 6.8. The solubility data of different formulations showed in **Table 2.** Co-processed excipients were prepared by incorporating one excipient into the particle structure of another excipient using a process such as co- drying. Thus they are simple physical mixtures of two or more existing excipients mixed at the particle level. We have found that co-processing of mannitol and microcrystalline cellulose leads to the formation of excipients granulates with superior

properties compared to physical mixtures of components or with individual components. Since mannitol has good aqueous solubility, negative heat of solution and good wetting properties we have combined it with highly compressible microcrystalline cellulose which is having good wicking and absorbing capacity. These attributes improve the binding of the tablet, increase the water uptake and thereby decrease the disintegration time of the tablets. Maarschalk has inferred that co-processing works well with a large amount of brittle materials and a small amount of plastic material as exemplified by cellactose. This combination prevents the storage of too much elastic energy during compression, which results in a small amount of stress relaxation and a reduced tendency for capping and lamination. A combination of plastic and brittle materials is necessary for optimum tableting performance by selectively overcoming the individual disadvantage. Such combination can help improve functionalities such as compaction performance, flow properties, strain rate sensitivity, lubricant sensitivity or sensitivity to moisture, or reduced hornification. From the results co-processed particles with 2:1 ratio with mannitol showed grater solubility when compared to other, by increasing the carrier concentration the solubility also increased proportionally. From all the above formulations, MCP2 formulation showed highest solubility in ASS phosphate buffer pH 6.8. The percent practical yield obtained for formulation MCPs1, MCPs5 were 90.12 - 98.23% respectively. The DSC thermogram of mannitol showed sharp endothermic peak at 171.12°C and monteleukast mannitol:HPMC co-processed particles shows two endothermic peaks corresponding to the melting point of drug and mannitol indicating no chemical interaction between them **(Figure 1 – 2)**. The SEM photographs describes that monteleukast are small crystalline structure but its original one was totally amorphous and no sign of crystallinity was observed in SEM photographs **(Figure 3)**.

Evaluation of Fast Dissolving Tablets: Monteleukast containing co-processed particles were direct compressed to formulate fast dissolving tablets. The pre-compression parameters showed that the powder blends had sufficient flow properties as per the approved limits. The thickness of the tablets was uniform in each batch. This showed that uniform compression force was applied while punching the tablets. The uniformity in weight is related to the improvement in powder flow properties through the addition of talc and magnesium stearate, resulting in effective die cavity filling **(Table 3)**. The MFTs were generally expected to have hardness of 5 to 5.5 kg/cm^2, since harder tablets are known to have longer disintegration times.

The hardness was monitored at regular intervals during punching to keep the hardness value at a uniform level. A deviation from the hardness will result in differences in disintegration time. The tablets were highly stable to any external stress that might be involved during transportation and packaging: the friability values were consistent with the USP limit of < 1 %. The results of the disintegration test, wetting time and dispersion time was less than 60 sec., which mimics the disintegration taking place in mouth, correlated with the results of the USP disintegration test. The result was indicated that the formulation was disperse within a minute and followed the need of purpose **(Table 4 – 5)**. Formulation MFDTs3 has the best dissolution profile of 94.38 % at 30 min **(Table 7.6 – 8.9)**. Results of in vitro dissolution studies were fitted to zero order, first order and Korsmeyer-Peppas equations. The values of r^2 ranged from 0.862 to 0.978 (first order plot) for different formulations **(Figure 4)**. The values of slope of Korsmeyer-Peppas plots ranged from 0.949 to 0.774. Addition of Monteleukast containing co-processed particles of mannitol:HPMC (2:1) ratio has water wicking and swelling properties which lead to rapid disintegration of drugs, which in turn, leads to the more rapid dissolution of drugs. Microcrystalline cellulose and mannitol in higher ratio act as superdispersible property and solubility enhancing agent. The combination of agents have more disintegrating property due to rapid water uptake and dispersion time which lead to rapid release of drug and made the dissolution faster. The results of the release kinetics study showed that all the formulations obeyed first order drug release profile more closely, i.e., the release rate depended upon the initial concentration of drug. The slope values of the Korsmeyer-Peppas plot showed that the mechanism was non-fickian or supercase II transport mechanism.

Conclusion: The proposed study is prepared and characterizes the fast dissolving tablet containing monteleukast co-processed particles (MCPs) formulation with using natural superdisintegrant with direct compression. The superdisintegrants and its concentration shall be during the preparation of MFDTs with monteleukast by using direct compression via employing different excipients in different ratio including: superdisintegrants {sodium starch glycolate (SSG), Ac-Di-Sol, crosspovidone (CP), Spray dried lactose which were used alone and in various combination and mannitol, along with lubricant and glidants. The prepared MFDTs with a short disintegration time, sufficient mechanical strength, better patient compliance, and acceptable stability profile by employing different methods of preparation

and studying different variables affecting pre and post-compression parameters. The pre-compression parameters showed that the powder blends had sufficient flow properties thickness was uniform and compression force was applied while punching the tablets. The uniformity in weight resulting in effective die cavity filling and hardness known to have longer deviation resulted in differences in disintegration time. The friability values were consistent and disintegration test, wetting time and dispersion time was less than 90 sec. The result was indicated that the formulation will be disperse within a minute and followed the need of purpose Formulation MFTs3 has the best dissolution profile of 99.99 % at 30 min. The in vitro dissolution studies were fitted to zero order, first order and Korsmeyer-Peppas equations. The addition of co-processed particles containing drug and Mannitol : HPMC (2:1) ratio has water wicking and swelling properties which lead to rapid disintegration of drugs, which in turn, leads to the more rapid dissolution of drugs. The combination of agents have more disintegrating property due to rapid water uptake and dispersion time which lead to rapid release of drug and made the dissolution faster. The results of the release kinetics study showed that all the formulations obeyed first order drug release profile more closely, i.e., the release rate depended upon the initial concentration of drug.

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Table 1: Preparation of MCP3 containing Monteleukast Fast Dissolving Tablets

Excipients (mg)	**MFDTs1**	**MFDTs2**	**MFDTs3**
Fast dissolving co-processed excipients ML: MCC (2:1)	200	200	200
SSG (Sodium starch glycollate)	20	40	30
Ac-Di-Sol	40	20	30
Spray dried lactose	50	50	50
Corn starch (anti-adherent)	25	25	25

Aspartame sodium (sweetening agent)	15	15	15
Crosspovidone (5%)	10	10	10
Magnesium stearate	5	5	5
Purified talc	5	5	5
Total amount (mg)	370	370	370

Table 2: Solubility study of taste masking of monteleukast by co-processed particles

S. No	**Medium**	**Solubility (mg/ml)±SD***		
		MCP1	**MCP2**	**MCP3**
1	Distilled water	1.351±0.51	1.480±0.11	1.568±0.11
2	0.1N HCI,	0.708±0.17	0.991±0.13	0.822±0.15
3	ASA pH 6.8 Phosphate buffer	1.521±0.28	1.999±0.17	1.711±0.31
4	Phosphate buffer pH 7.4	1.432±0.17	1.718±0.11	1.611±0.18

Table 3: Flow properties of granules of Fast Dissolving Tablets blends (MFDTs1 – MFDTs3)

Formulation code	**Carr's index [n] (%)**	**Hausner's ratio [n]**	**Angle of repose (θ) [n]**
MFDTs1	18.01±0.002	1.17±0.011	26.1±0.001
MFDTs2	17.04±0.011	1.17±0.001	29.1±0.001
MFDTs3	18.03±0.013	1.15±0.028	28.8±0.002

n = 3 (mean ± Standard deviation)

Table 4: Physical characterization of fast dissolving tablets (MFDTs1 – MFDTs3)

Formulation code	**Tablet Thickness (mm)**		**Weight Variation**	**Hardness (kg/cm ^{2})**	**Friability w/w (%)**
	Diameter	**Height**			

			(%)		
MFDTs1	8.01±0.001	2.11±0.002	2.1±0.011	3.6±0.12	0.614±0.005
MFDTs2	8.02±0.002	2.04±0.011	2.2±0.031	4.1±0.19	0.515±0.002
MFDTs3	8.01±0.001	2.01±0.011	2.1±0.002	4.9±0.21	0.493±0.002

n = 3 (mean ± Standard deviation)

Table 5: Physical characterization of fast dissolving tablets (MFDTs1 – MFDTs3)

Formulation code	**Drug Content (%)**	**Disintegration Time (sec)**	**Wetting time (sec)**	**Water absorption ratio (%)**	**Dispersion Time (sec)**
MFDTs1	99.2±0.10	51±0.01	21.01±0.09	28.11±1.02	33±0.02
MFDTs2	99.1±0.05	42±0.03	16.22±0.03	23.61±1.13	31±0.01
MFDTs3	99.8±0.01	31±0.03	11.00±0.03	19.31±1.42	32±0.02

n = 3 (mean ± Standard deviation)

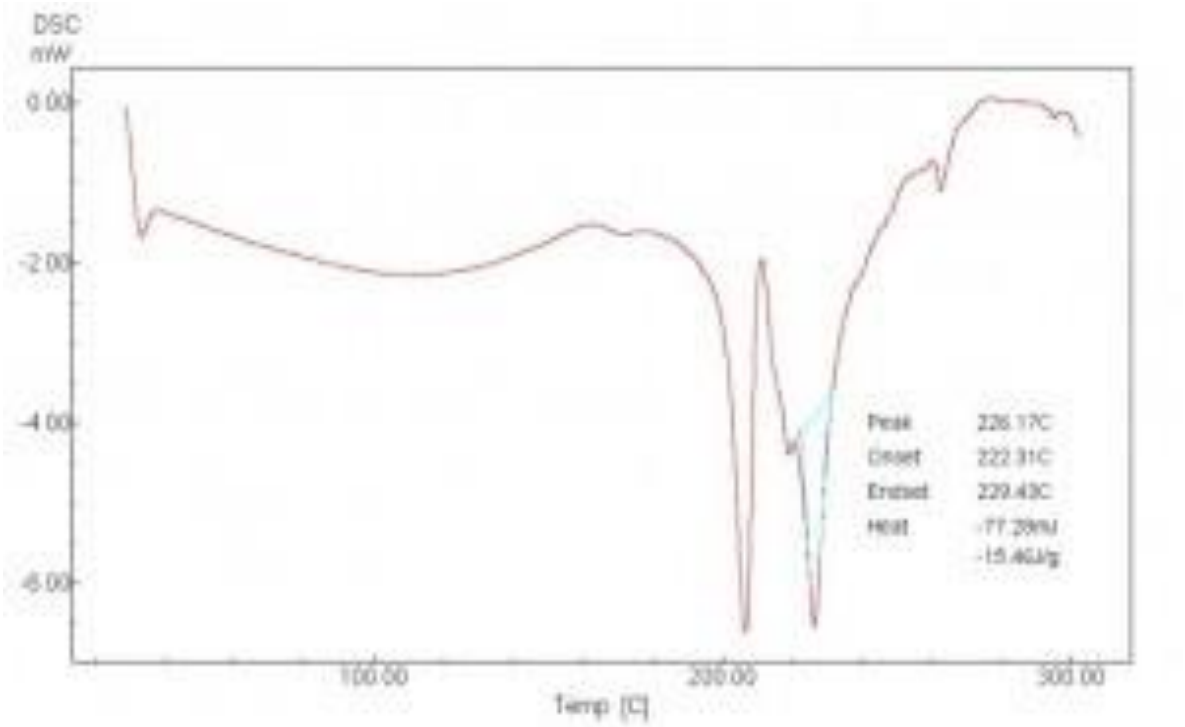

Figure 1: DSC of drug sample (S1)

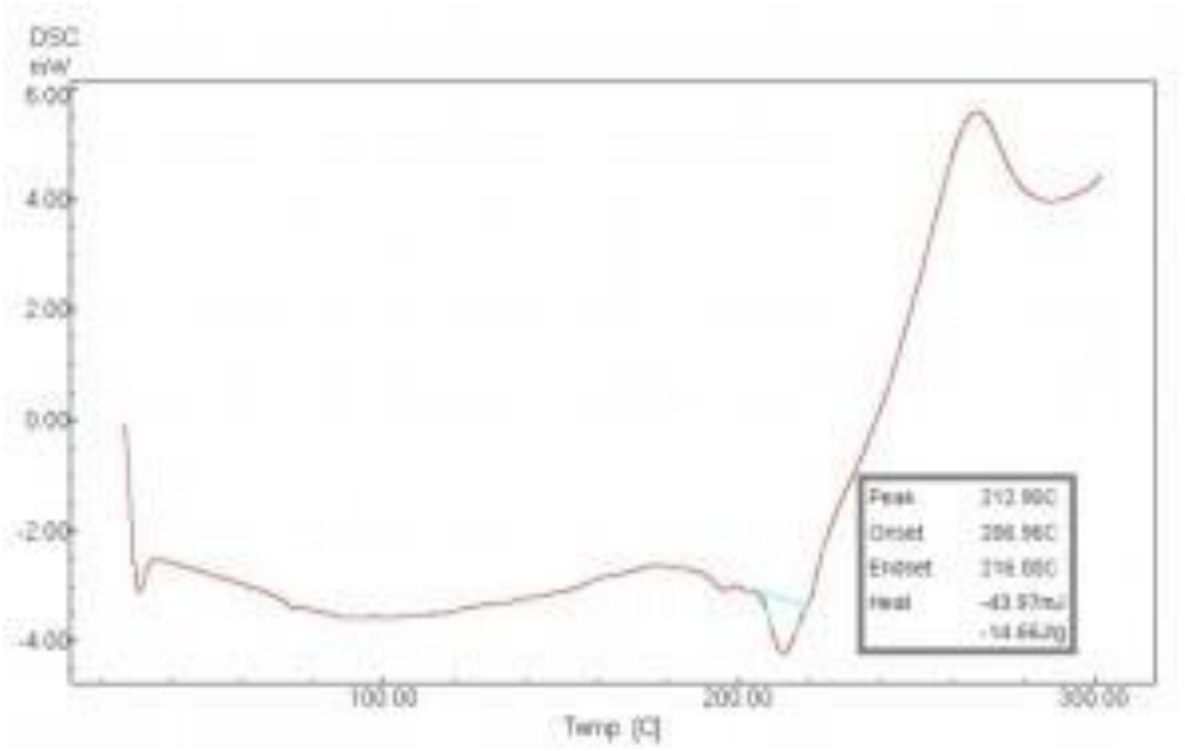

Figure 2: DSC of drug and all excipients (MCP2)

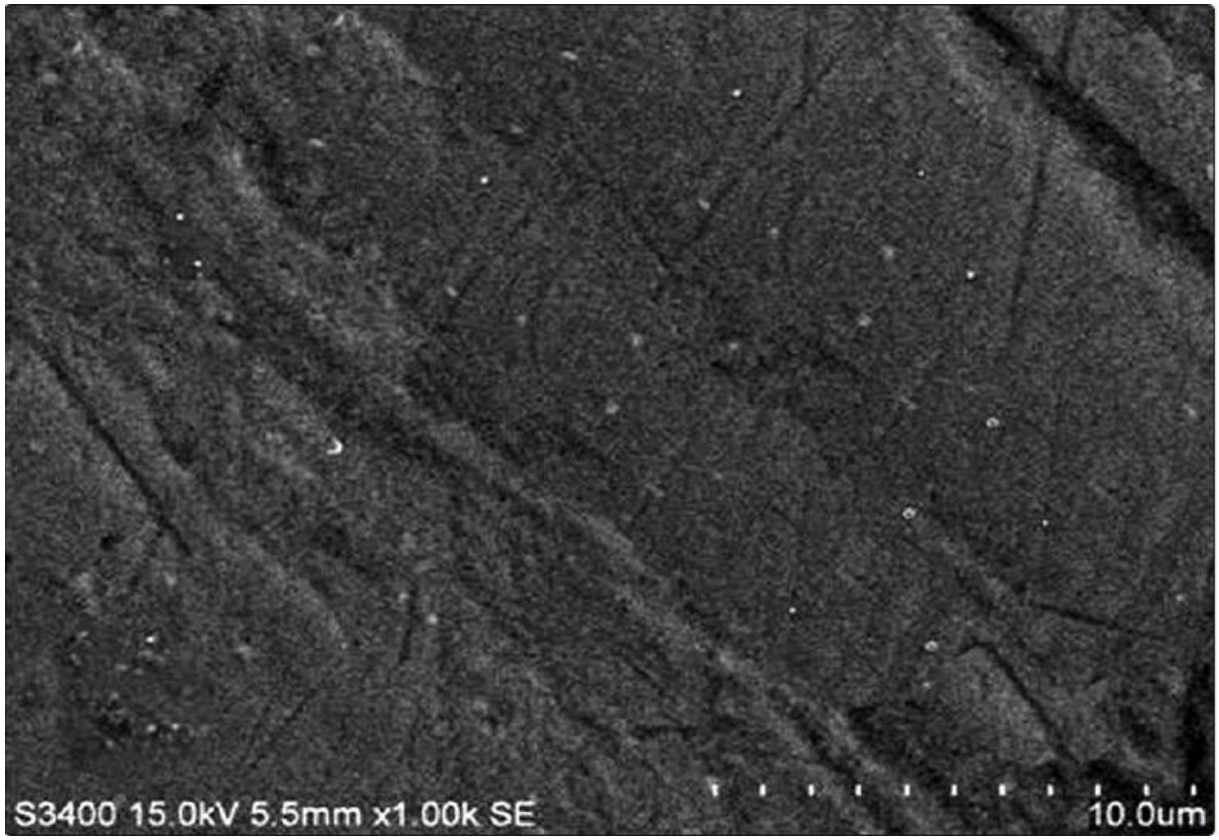

Figure 3: SEM photograph of drug co-processed particles (MCP2)

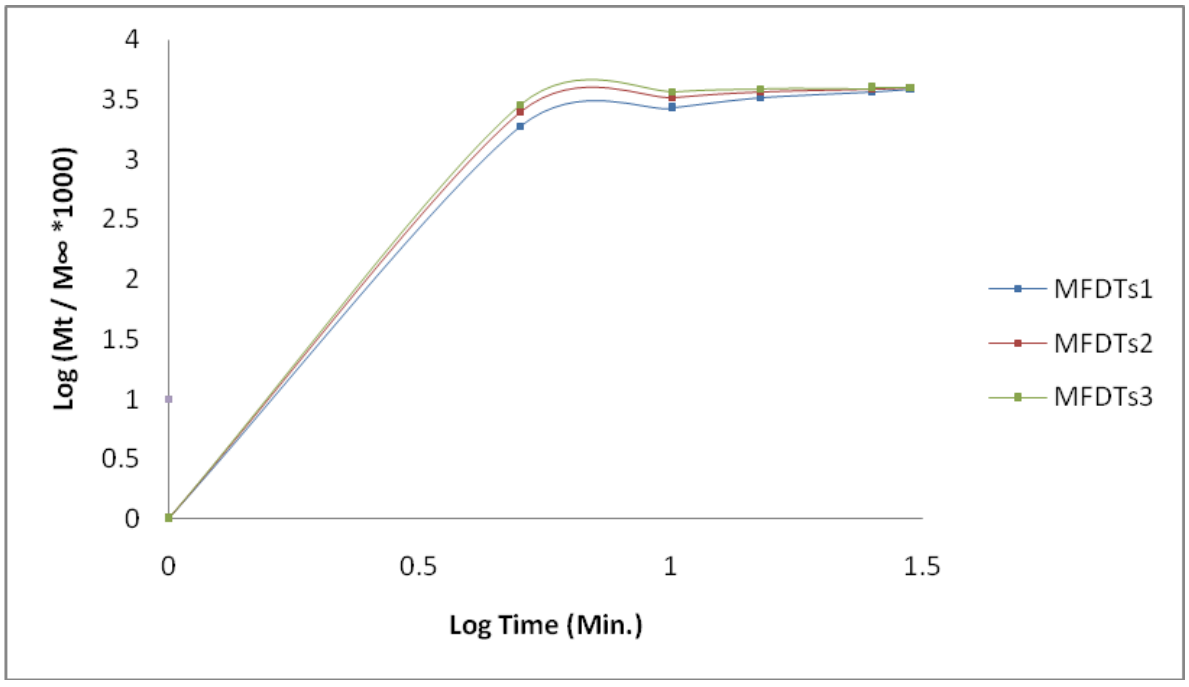

Figure 4: Korsmeyeyr's Peppas plots of fast dissolving tablets (MFDTs1 – MFDTs3)