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Formulation and Evaluation of Meclofenamate Fast Dissolving Tablet

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A B S T R A C T

The study of this work was to use a swellable polymer chosen among superdisintegrants, for improving the dissolution rate of a sparingly soluble drug, loaded on its surface. Meclofenamate, which has very low water solubility, was chosen as a model drug, while cross linked sodium carboxymethyl cellulose (Ac-Di-Sol) was chosen as the swellable polymer. The Drug Polymer systems were prepared using direct compression method. The results of the dissolution tests showed that the dissolution rate of Meclofenamate from the systems prepared increase, particularly in the case of the preparation composed of Ac-Di-Sol plus surfactant agents. Attempts were made to increase the rate of drug release (disintegration) to enhance the in vitro dissolution of the poorly soluble drug by using extra, intra and partly intra and extra granular method of addition of sodium starch glycolate as superdisintegrants and to develop a stable immediate release formulation by direct compression method.

Key Words: Fast dissolving tablet, disintegrants, Meclofenamate Sodium, sodium starch glycolate

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INTRODUCTION

Oral route is the most preferable and convenient route of administration as it offers advantages like ease of administration, highly versatile, patient compliance and accurate dosing[1]. The most popular solid dosage forms are being tablets and capsules. One important drawback of these dosage forms for some patients, is the difficulty to swallow and readily access to water for easy swallowing dosage[2]. Difficulty in swallowing (dysphasia) is also a common problem of all age groups, especially the elderly and paediatrics, because of physiological changes associated with these groups[3]. Fast dissolving drug delivery is rapidly gaining acceptance as an important new drug delivery technology which aims to enhance safety and efficacy of drug molecule by formulating a convenient dosage form for administration and to achieve better patient compliance[4]. The fast dissolving tablet (FDT) has remarkable disintegration properties and it can rapidly disintegrate without water in the mouth within few seconds. When an FDT is placed in the oral cavity, saliva quickly penetrates into the pores causing rapid disintegration. Meclofenamate Sodium is the sodium salt form of potent NSAID Meclofenamate sodium, an anthranilic acid and non-steroidal anti-inflammatory drug (NSAID) with antiinflammatory, antipyretic and analgesic actions. Meclofenamate sodium acts inhibiting the activity of the enzymes cyclo-oxygenase I and II, which decreased the formation of precursors of prostaglandins and thromboxanes. Meclofenamate sodium is also used for the treatment of primary dysmenorrheal (painful menstrual periods) and for the treatment of idiopathic heavy menstrual blood loss. It undergoes rapid first-pass metabolism in the liver (approximately 95% of a dose). This leads to lower bioavailability of Meclofenamate Sodium. Such drugs shows first-pass metabolism effect, so the drug is selected for fast dissolving tablet.[5-10]

Materials and methods

Material

Meclofenamate Sodium was received as gift sample by Pro Lab Marketing Pvt. Ltd., Delhi, Magnesium stearate used were procured from Reckon animal health care, Jaipur ,Banana powder was gifted by Ayursatva, Madhya-Pradesh, Asparteme used was procured from Sweetener India, Delhi, and other reagents and chemicals used were of analytical grade.

Method

Fast dissolving tablet of Meclofenamate Sodium were prepared by direct compression method. Pure drug and excipients were passed through # 60 no. mesh, required amount of drug and excipients were taken for every formulation (Table No. 1). The powdered drug, Mannitol and Lactose were mixed uniformly with continuous trituration using mortar and pestle. Then weighed quantity of super disintegrates and aspartame taken for each formulation and properly mixed, finally magnesium stearate and talc powder were added and mixed well. The mixed blend of drug and excipients were compressed using 10 station tablet punching machine. (Shakti pharmaceuticals). A Batch of 50 tablets of each formulation was prepared for all the designed tablet formulations. Before the tablet preparation /punch the mixture blend of all designed formulations were subjected to compatibility studies (IR) and pre-compression parameters like- Angle of repose, Bulk density, Tapped density, compressibility index, Hauser's ratio.[11-12]

Preparation of fast dissolving tablet of Meclofenamate

The critical parameters to formulate fast dissolving tablet are choice of super disintegrants and optimization of concentration of superdisintegrants. The main criteria for fast dissolving tablets is to disintegrate or dissolve rapidly in oral cavity in 15-60 seconds, without need of water and should have pleasant mouth feel. The Fast dissolving tablet of Meclofenamate are prepared by using direct compression method with the incorporation of superdisintegrants like Microcrystalline cellulose (MCC), Sodium starch glycolate, Croscarmellose Sodium (CCS), with Meclofenamate equivalent to 8 mg, Mannitol and Microcrystalline Cellulose are mixed thoroughly in glass mortar using a pestle. Superdisintegrants were incorporated in the powder mixture according to each formulation in the tablets and finally Aspartame, and Magnesium stearate and flavour was added. The whole mixture was passed through Sieve No. 60 twice. Tablets were prepared by using Shakti Pharmatech 10 station punching machine. The compression force was constant during Punch.

Table 1: Meclofenamate Fast Dissolving Tablets by direct compression method

Ingredients (mg)	**F1**	**F2**	**F3**	**F4**	**F5**	**F6**	**F7**	**F8**	**F9**
Meclofenamate	100	100	100	100	100	100	100	100	100
Cross carmellose Sodium	3	6	9	-	-	-	-	-	-
Sodium Starch Glycolate	-	-	-	3	6	9	-	-	-
Crosspovidone	-	-	-	-	-	-	3	6	9
Aspartame	1.5	1.5	1.5	1.5	1.5	1.5	1.5	1.5	1.5
Flavour	1.5	1.5	1.5	1.5	1.5	1.5	1.5	1.5	1.5
Talc	1.5	1.5	1.5	1.5	1.5	1.5	1.5	1.5	1.5
Magnesium Stearate	1.5	1.5	1.5	1.5	1.5	1.5	1.5	1.5	1.5
Mannitol	20	17	14	20	17	14	20	17	14
Lactose	21	21	21	21	21	21	21	21	21
TOTAL	**150**	**150**	**150**	**150**	**150**	**150**	**150**	**150**	**150**

Result and Discussion

In the proposal study fast dissolving tablets of Meclofenamate were prepared and evaluated for their use to obtain Fast release and to prevent first pass metabolism.

Analytical Profile of Meclofenamate:

The DSC thermogram of Meclofenamate is shown in Figure1: The DSC thermogram of Meclofenamate showed sharp peak at 279^{0}C. The identity of a compound was confirmed by comparison with that of an authentic sample and verification of the presence of functional groups in an unknown molecule was done by IR spectra**.** The IR spectra obtained was elucidated for important chromophore groups. The IR spectra showed peaks at 3311, 2924, 2854, 1651, 1511, 1163 and 551 cm^{-1}. The various peaks are depicted in Figure 2

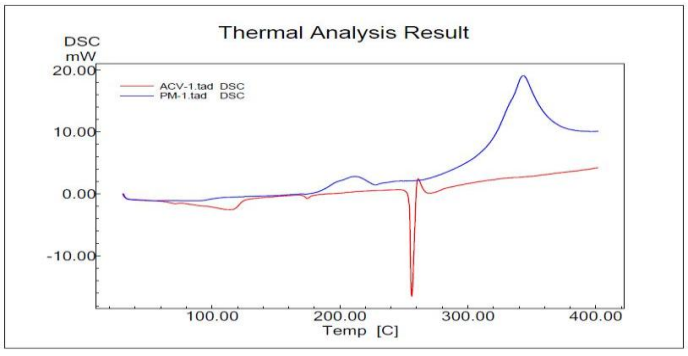

Figure 1: DSC Thermogram of Meclofenamate

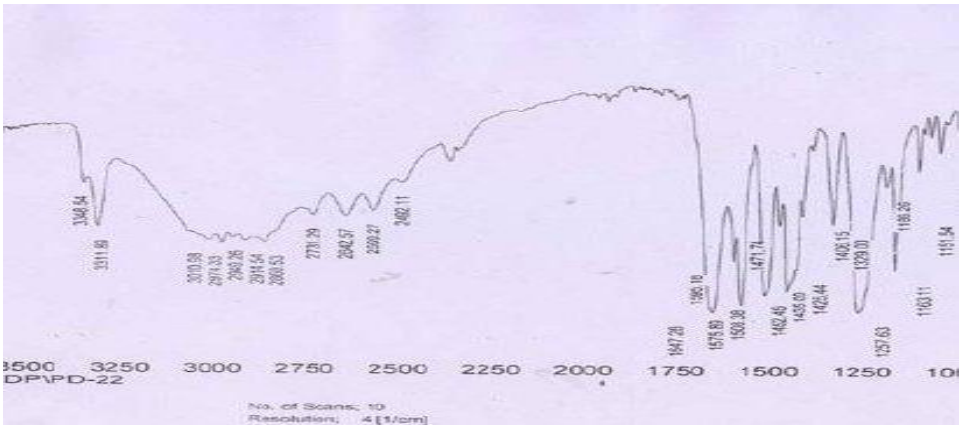

Figure 2: IR Spectra of Meclofenamate

Characterization of Fast dissolving tablets of Meclofenamate

On the characterization of the drug free tablet the best formulations were selected and the drug Meclofenamate was incorporated in these formulation. The characterization of mixed blend done for the flow property of powder that are bulk density, tapped density, angle of repose, Compressibility index, Hausner's ratio were shown in Table 1

. Table 1: Characterization of blend of Meclofenamate tablet

Formulation	Bulk Density (mg/ml)	Tapped Density (mg/ml)	Hausners Ratio	Compressibilty Index (%)	Angle of Repose
F_1	0.591±0.12	0.621±0.11	1.180±0.05	14.25±0.15	24.19±1.38
F_2	0.521±0.11	0.616±0.69	1.100±0.09	15.89±0.23	25.32±1.35
F_3	0.531±0.18	0.495±0.54	1.101±0.19	16.28±0.28	24.45±1.40
F_4	0.551±0.17	0.642±0.22	1.171±0.15	14.87±0.55	24.52±0.55
F_5	0.540±0.05	0.592±0.29	1.161±0.19	15.98±0.63	25.11±1.25
F_6	0.551±0.11	0.692±0.27	1.175±0.58	16.89±0.89	24.19±1.89
F_7	0.501±0.15	0.551±0.10	1.170±1.01	15.05±0.25	25.29±0.15
F_8	0.500±0.01	0.561±0.19	1.171±1.12	15.10±0.55	25.20±0.29
F_9	0.502±0.12	0.591±0.11	1.161±1.14	14.20±0.56	25.32±1.11

The prepared drug tablets were evaluated as similar as the drug free tablets. After compression of powder the tablet were evaluated for physical organoleptic characteristics like colour, odour, taste, diameter, Thickness, Hardness, Friability, dispersion time, Disintegration time, wetting time.

All the formulations were exhibit in white colour, odorless, convex in shape with smooth surface with zero defects. The average weight of the prepared tablet was found 145.07 to 154.05 mg. The thickness of the tablet was found 3 mm. The diameter of the tablets was found to be 4 mm. The hardness of the prepared tablet varied from 3.01 to 3.20 Kg/cm^2. Which have satisfactory strength to withstand the mechanical shocks. The friability of all the formulation was found to be less than 1.0 %. The results shows resistance to loss of weight indicates the tablet's ability to withstand abrasion in handling, packaging and shipment. The disintegration time of the tablets was varied from 30 to 69 seconds. The in vitro swelling time of all the formulations were varied between 14 to 22 seconds.

Table 2: Characterization of Meclofenamate fast dissolving tablet

Formulation	Diameter (mm)	Thickness (mm)	Weight (mg)	Hardness (Kg/cm^2)	Friability (%)	Disintegration Time (Sec)	Swelling (Sec)
F_1	4	3	154.05±0.55	3.05±0.15	0.48±0.84	44±1.44	15±1
F_2	4	3	145.07±0.78	3.09±0.01	0.59±0.25	39±1.14	14±2
F_3	4	3	147.01±0.11	3.14±0.99	0.57±0.17	45±1.46	16±1
F_4	4	3	152.02±0.25	3.10±0.12	0.51±0.16	63±1.25	21±1
F_5	4	3	154.01±0.11	3.08±0.01	0.69±0.12	69±1.52	22±2
F_6	4	3	152.05±0.15	3.20±0.10	0.75±0.32	49±1.36	17±2
F_7	4	3	150.01±0.15	3.15±0.05	0.65±0.13	31±1.01	13±2
F_8	4	3	150.00±0.04	3.01±0.09	0.62±0.23	30±1.59	12±2
F_9	4	3	147.02±0.22	3.20±0.28	0.38±0.19	33±1.58	13±8

The drug content of all the formulations was determined spectrophotometrically at 279 nm. It varied from 139.66 to 147.96 mg per tablet.

Table 3: Drug Content in the Fast Dissolving Tablet of Meclofenamate

Formulation	Drug Content (mg per Tablet)	% Drug Content
F_1	139.66±0.025	93.11
F_2	142.83±0.041	95.22
F_3	140.32±0.125	93.55
F_4	141.33±0.720	94.22
F_5	145.20±0.385	96.28
F_6	141.37±0.251	94.25
F_7	145.33±0.558	96.89
F_8	147.96±0.385	98.64
F_9	146.25±0.250	97.50

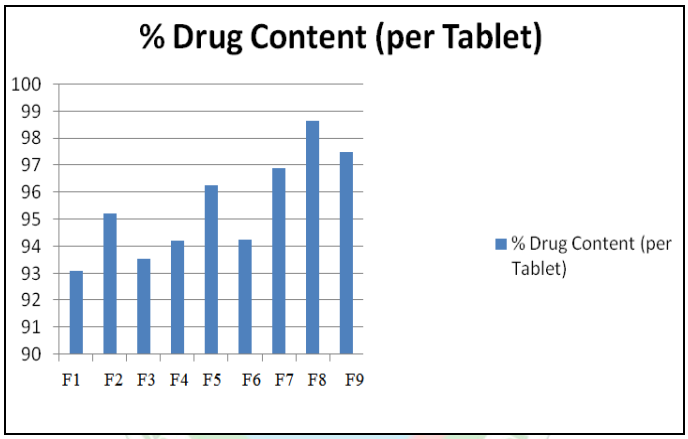

Figure 3: Drug Content in the Fast Dissolving Tablet of Meclofenamate.

In vitro Drug release profile

In vitro drug release profile experiments were performed at 37± 1°C in six basket dissolution rate apparatus LAB INDIA DS 8000. The data obtained in *in- vitro* Drug release study are tabulated and represented graphically as:

Drug release study are tabulated and represented graphically as:

- Cumulative percentage drug release v/s time (zero order release kinetic)
- Log cumulative percentage drug retained v/s time (First order release kinetics)
- Cumulative percentage drug release v/s square root of time (Higuchi model)
- Log cumulative percentage drug release v/s Log time (Kosmeyer data curve).

The results showed that all the formulation releases the drug within 1 to 3 minutes. The maximum drug release was found in formulation F_8 (98.64%). The order of drug release was found to be:

$F_8 > F_9 > F_7 > F_5 > F_2 > F_6 > F_4 > F_3 > F_1$

The rapid drug dissolution might due to easy breakdown of particles and rapid absorption of drug into the dissolution medium.

Next the release data obtained were subjected for the kinetic treatment to know the type and order of drug release. From the in-vitro drug release profile it is evident that the kinetics of drug release is first order for all the prepared fast dissolving tablets as the plot between log percent drug retained versus time showed good linearity. The coefficient of determination of R^2 values much closer to 1 for the higuchi plots, thus indicating the drug release from the tablets followed a diffusion controlled mechanism. The value of n obtained from Kosemeyer curves was in the range of near to one which is a further indication of the diffusion-controlled release.

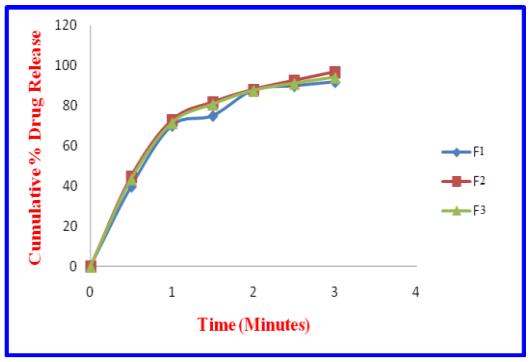

Figure 4: In vitro release curve of Meclofenamate tablet -Zero Order Release

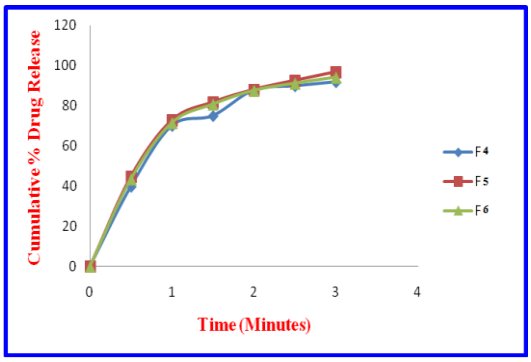

Figure 5: In vitro release curve of Meclofenamate tablet -Zero Order Release

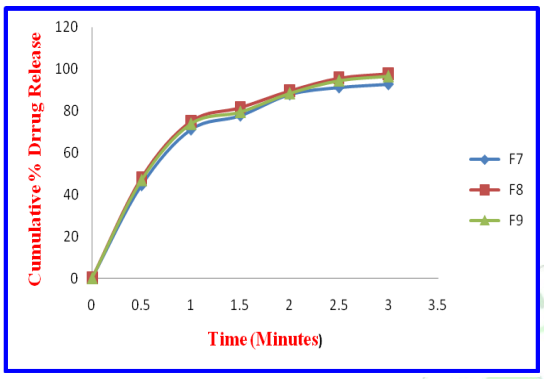

Figure 6: In vitro release curve of Meclofenamate tablet -Zero Order Release

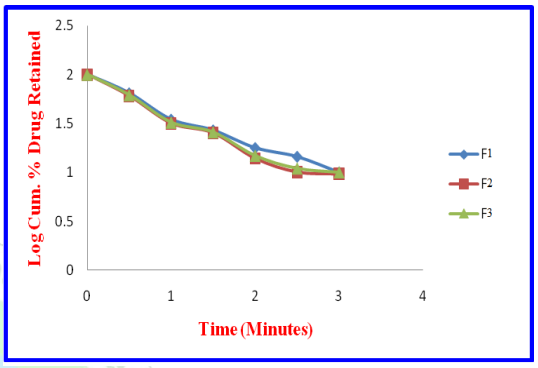

Figure 7: In vitro release curve of Meclofenamate tablet -First Order Release

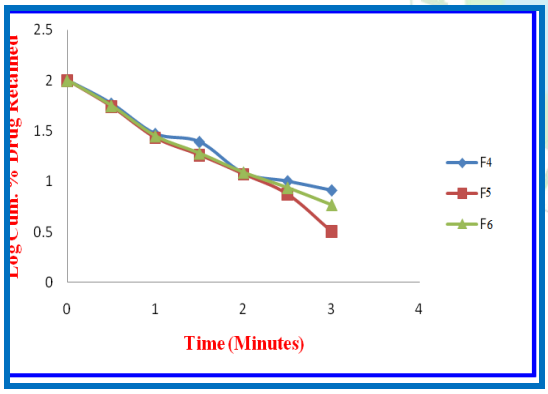

Figure 8: In vitro release curve of Meclofenamate tablet -First Order Release

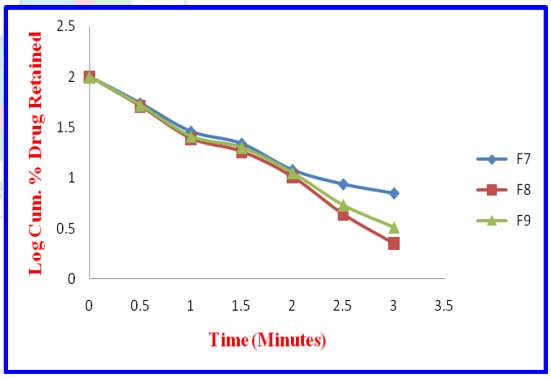

Figure 9: In vitro release curve of Meclofenamate tablet -First Order Release

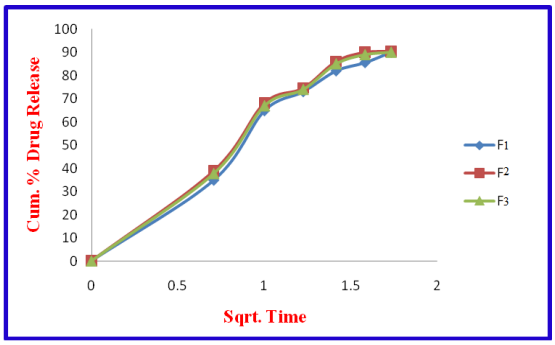

Figure 10: In vitro release curve of Meclofenamate tablet - Higuchi Model

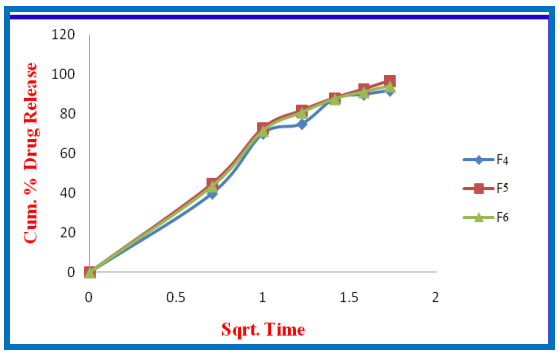

Figure 11: In vitro release curve of Meclofenamate tablet - Higuchi Model

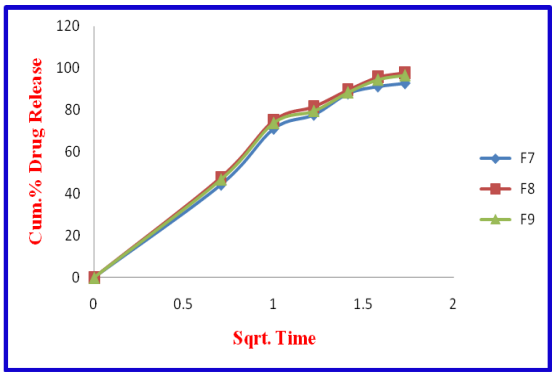

Figure 12: In vitro release curve of Meclofenamate tablet - Higuchi Model

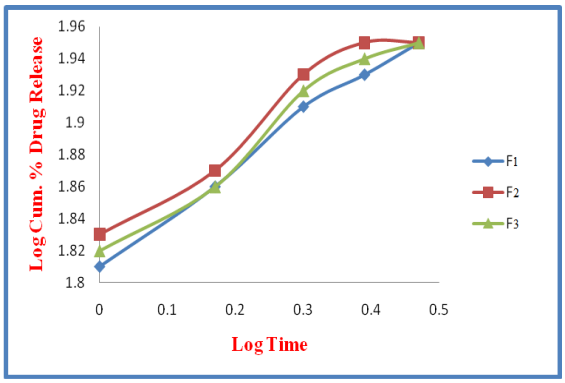

Figure 13: In vitro release curve of Meclofenamate tablet - Korsemeyer Model

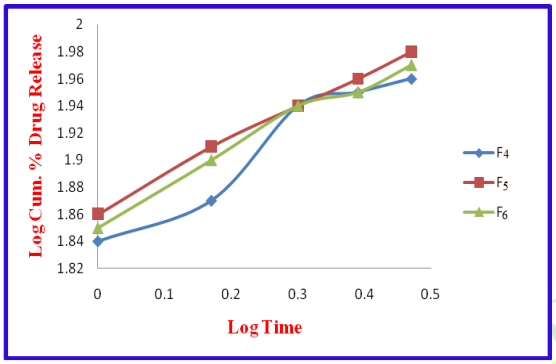

Figure 14: In vitro release curve of Meclofenamate tablet - Korsemeyer Model

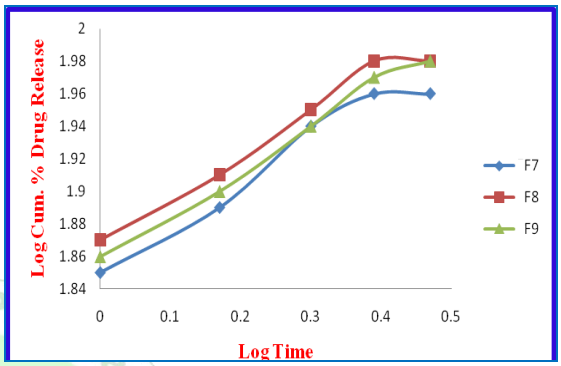

Figure 15: In vitro release curve of Meclofenamate tablet - Korsemeyer Model

Next the Release data obtained were subjected for Kinetic treatment to know the type and order of drug release. From the in-vitro drug release profile it is evident that the kinetic of drug release is first order for all the prepared fast dissolving tablets as the plot between log percent drug retained versus time showed good linearity. The coefficient of determination of R^2 values much closer to 1 for Higuchi plots, thus indicating the drug release from the tablets followed a diffusion controlled mechanism. The permeation Kinetics data are shown in table 4

Table 4: Fit of Various Kinetic Models for Fast Dissolving Tablet of Meclofenamate

Formulation Code	Zero Order R^2	First Order R^2	Higuchi Model R^2	Korsemeyer Model R^2
F1	0.836	0.981	0.972	0.993
F2	0.815	0.964	0.966	0.952
F3	0.821	0.967	0.969	0.973
F4	0.796	0.965	0.963	0.941
F5	0.807	0.989	0.965	0.996
F6	0.791	0.985	0.962	0.984
F7	0.790	0.977	0.963	0.959
F8	0.789	0.992	0.964	0.974
F9	0.795	0.990	0.966	0.991

Figure 16: Different stages of Disintegration of Fast Dissolving Tablet

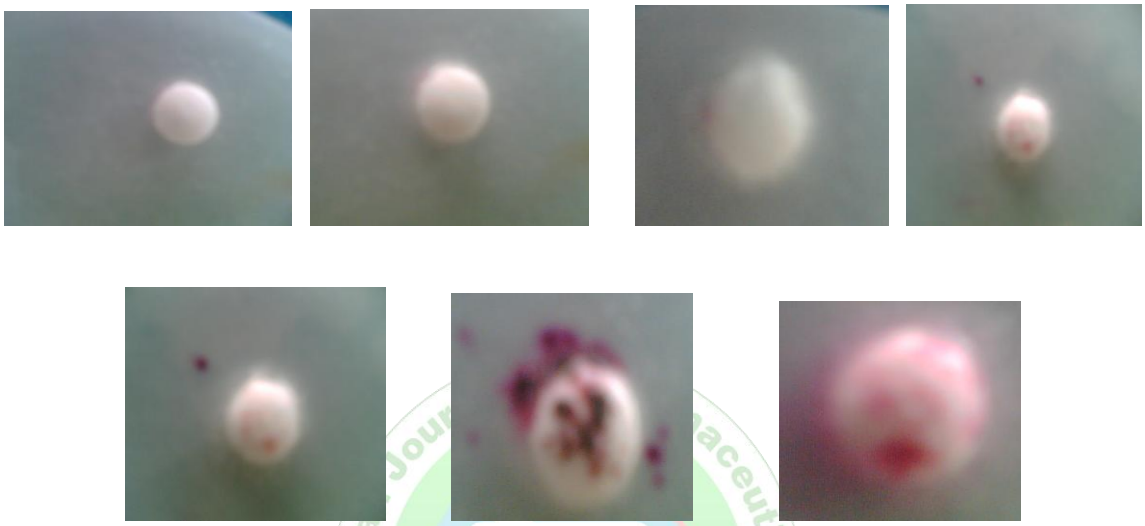

Figure 17: Different stages of Swelling of Fast Dissolving Tablet

SUMMARY

Today we are planning of developing unique delivery system for immediate release of drugs only due to recent advances in technology. In the present study fast dissolving tablet of Meclofenamate was formulated, prepared and evaluated for all the standards. The formulated tablets, which can disintegrate or dissolve rapidly once placed into the oral cavity. The tablet is the most widely used dosage form because of its convenience in terms of self administration, compactness and ease in manufacturing. However, geriatric and pediatric patients experience difficulty in swallowing conventional tablets, which leads to poor patient compliance. To overcome this weakness, we have developed innovative drug delivery system known as "mouth dissolving tablet or oral melt tablet". These are novel type of tablets that dissolves in saliva. There characteristics advantages such as administration without water, anywhere, anytime lead to their suitable place to geriatric and pediatric patients. They are also suitable for the mentally and psychotic ill, the bedridden and patient who do not have easy access to water. The benefit in terms of patient compliance, rapid onset of action, increased bio-availability and good stability make these tablets popular as a dosage form for the treatment of muscle spasm and tone.

Meclofenamate is used for the treatment of mild to moderate pain from various conditions (Dental pain, Osteoarthritis pain and Menstrual Pain) and to decrease blood loss from menstrual periods.

The biological half-life (2-3 hours) is very short and therefore it is an ideal drug candidate for rapid release drug delivery system.

The objective was to fabricate the fast dissolving tablet for rapid release of drug, their characterization, and in-vitro drug release studies. The Meclofenamate drug was analyzed by IR, DSC, solubility, partition coefficient, maxima wavelength. The drug sample was found to comply with all the specifications.

In the Present investigation the solubility of poorly water soluble Meclofenamate was enhanced by using Polymer. Appropriate quantity of Polymers was blended with super disintegrants, after adding sweetener, glidant and lubricating agent fast dissolving tablets were prepared by using direct compression method with the help of Shakti pharmatech tablet punching machine.

From the above experimental finding it can be concluded that:

Pre-compression parameters

- Bulk Density and Tapped Density of the Blend were found as 0.501 to 0.590 and 0.490 to 0.690 respectively.
- Carr's index of the prepared blend fall in the range of 14.20 to 16.89% and this is also supported by Hausner's factor values which were in the range of 1.100 to 1.181.Hence the prepared blends posses good flow property and can be used for manufacturing of the tablet.
- The values of angle of repose were found in the range of 24.19 to 26.53.

Post-compression Parameter

All the tablets were prepared under similar experimental conditions. All the formulation exhibited white colour, odourless, flat shaped with almost smooth surfaces.

- The average weight of the fast dissolving tablet was 145.07 to 154.11mg.
- Hardness of prepared tablet was between 3.01 to 3.20 kg/cm^2
- The percent friability of formulations was found to be 0.38 to 0.75 (less than 1.0%) and thus hardness and friability of all formulation are found within acceptable limits.
- The disintegration time is very important and it is desired to be less than 1 minute. The quick disintegration may assist quick swallowing and drug absorption in buccal cavity, thus greater bioavailability of the drug. Disintegration time of prepared fast dissolving tablet was found in the range of 30 to 69 seconds.
- Swelling time is the indicator for the ease of disintegration of the tablet in the buccal cavity. It was observed that swelling time of tablet was in the range of 14 to 25 seconds. It was found that the nature of superdisintegrants present affected the swelling of the tablets.
- Assay of the prepared formulation was performed to determine drug content uniformity and it was found between 94.89 to 98.64%.

In Vitro dissolution study: In vitro dissolution study was performed by using Phosphate buffer pH 7.4 as dissolution medium using dissolution test apparatus LAB INDIA DS 8000 at a paddle speed of 50 rpm. At the end of 5 minutes the cumulative percentage drug release from various fast dissolving tablets of Meclofenamate was found to be 98.64%, 97.50%, 96.89%, 96.28%, 95.22%, 94.25%, 94.22%, 93.555% and 93.11% from F8, F9, F7, F5 F2, F6, F4, F3 and F1 respectively. Crosspovidone superdisintegrant provides maximum release of the drug. The release of drug followed first order kinetics and mechanism of drug release was found to be diffusion controlled.

$$F_8 > F_9 > F_7 > F_5 > F_2 > F_6 > F_4 > F_3 > F_1$$

Drug-excipient interaction study: Drug excipient interaction study was performed using FTIR spectrophotometer (KBr press model SHIMADZU FTIR-5300, Japan) the pressed pellets of kneaded mixture of drug and excipient was prepared and scanned, there was no evidence of interaction of excipient with the drug.

CONCLUSION

From the above experimental findings it can be concluded that:

- Fast dissolving tablets prepared by the Natural superdisintegrants are promising for rapid release of Meclofenamate.
- Incorporation of one super disintegrants in another in a definite concentration enhanced the release rate of Meclofenamate but when the concentration of superdisintegrants is increased from its maximum concentration it decrease the release profile of drug and thus therapeutic levels of the drug could be achieved through fast dissolving tablets.
- Prepared tablets exhibited first order kinetics and the drug release profile was matrix diffusion type.
- From this study it is possible to design suitable fast dissolving tablets containing Meclofenamate for the treatment of Pain and heavy blood loss with more effectiveness and better patient compliance.

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