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PREPARATION AND EVALUATION OF FAST DISSOLVING TABLETS OF ACAMPROSATE CALCIUM USING CO PROCESSED METHOD

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ABSTARCT

In the present work, an attempt has been made to develop fast dissolving tablets of Acamprosate calcium using co processed super disintegrates technology was employed to formulate the tablets. All the formulations were prepared by direct compression method. The blend of all the formulations showed god flow properties such as angle of repose, bulk density, tapped density. The prepared tablets were shown good post compression parameters and they passed all the quality control evaluation parameters as per I.P limits. Among all the formulations F10 formulation showed maximum drug release at 15 min hence it is considered as optimised formulation.

KEYWORDS: Acamprosate calcium, Co processed super disintegrates, Fast dissolving tablets.

INTRODUCTION

The oral route of administration is considered as the most widely accepted route because of its convenience of self administration, compactness and easy manufacturing. But the most evident drawback of the commonly used oral dosage forms like tablets and capsules is difficulty in swallowing, leading to patients incompliance particularly in case of paediatric and geriatric patients, but it also applies to people who are ill in bed and to those active working patients who are busy or travelling, especially those who have no access to water.[1]

For these reasons, tablets that can rapidly dissolve or disintegrate in the oral cavity have attracted a great deal of attention. Oral dispersible tablets are not only indicated for people who have swallowing difficulties, but also are ideal for active people.[2]

US FDA defined FDT tablets as "A solid dosage form containing medicinal substances which disintegrates rapidly usually within a matter of seconds, when placed upon the tongue".

Orally disintegrating tablets are also called as mouth-dissolving tablets, fast disintegrating tablets, fast dissolving tablets, Fast dissolving tablets, rapimelts, porous tablets, quick dissolving tablet.[3]

The US Food and Drug Administration responded to this challenge with the 2008 publication of Guidance for Industry: Orally Disintegrating Tablets.[4] Three main points stand out in the final guidance:

- FDTs should have an in vitro disintegration time of approximately 30sec or less.
- Generally, the FDT tablet weight should not exceed 500 mg, although the combined influence of tablet weight, size, and component solubility all factor into the acceptability of an FDT for both patients and regulators.
- The guidance serves to define the upper limits of the FDT category, but it does not supersede or replace the original regulatory definition mentioned. In other words, disintegration within a matter of seconds remains the target for an FDT.

Mechanism Of Action Of Fdt In Oral Mucosa

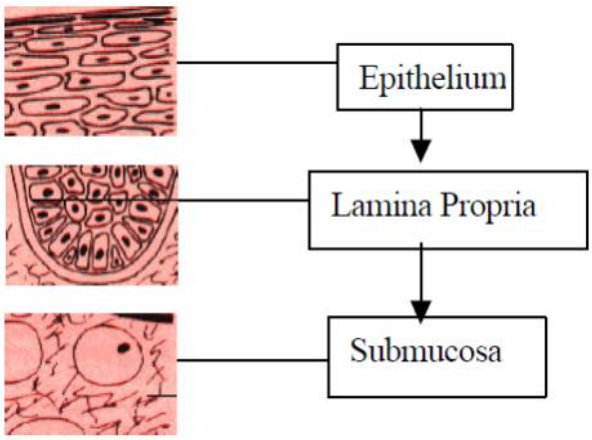

Fig: 1. Different layers of oral mucosa[5]

Mechanism of Action

The FDT is placed upon patient's tongue or any oromucosal tissue. It instantly get wet by saliva due to presence of hydrophilic polymer and other excipients,

then the tablet rapidly hydrates and dissolves to release the medication for oromucosal absorption

Various Technologies Used In Formulation of Fdt

The technologies that have been used by various researchers to prepare orally disintegrating dosage forms include: Patented and Non patented technologies.

Table.1 Patented and Non- patented technologies[6-19]

Non –patented	Patented
Freeze drying Spray drying Molding Phase transition process Melt granulation Sublimation Mass extrusion Cotton candy process Direct compression Nanonization Effervescent method	Zydus technology Orosolv technology Durosolv technology Wowtab technology Fashtab technology Oraquick technology Lyoc technology Quick –Dis technology Nanocrystal technology Frosta technology Pharmaburst technology Flash Dose technology Ziplet/Advatab technology QuickSolv technology

Criteria For Selection Of Drug To Develop Fdt[20]

An FDT may have varying degrees of pregastric absorption of drugs and thus, the pharmacokinetic profiles of drugs will vary, therefore, the FDTs will not be bioequivalent to the conventional dosage forms.

The ideal characteristics of a drug to develop as an FDT include:

- No bitter taste.
- Small to moderate molecular weight.
- Good stability in water and saliva.
- Partially non-ionized at the oral cavities pH.
- Ability to permeate oral mucosal tissue

Unsuitable drug characteristic for FDTs:

- Short half-life and frequent dosing.
- Very bitter or otherwise unacceptable taste because taste masking cannot be achieved.
- Required controlled or sustained release.

Selection Of Super Disintegrants

Super disintegrants not only affect the rate of disintegration, but when used at higher concentrations they also affect mouth feel, tablet hardness and friability [21]. Hydrotropic agents are selected according to critical concentration of disintegrant. Below this concentration, the tablet disintegration time is inversely proportional to the concentration of the Hydrotropic agent .Hence, various ideal characteristics of super disintegrants should be considered while selecting for a particular formulation.

- Produce rapid disintegration.
- Be compactable enough to produce less-friable tablets.
- Produce good mouth feel to the patient. Thus, small particle size is preferred to achieve patient's compliance
- Should have good flow properties to improve the flow ability of the total blend.

Taste Masking Approaches For Fdts[22]

Mouth dissolving tablet, which disintegrate or dissolve in the saliva produce a positive or negative taste sensation. Most of the drugs have unpalatable taste in which taste masking plays critical role in formulating FDT. The negative taste sensation of drugs can be reduced or eliminated by various approaches which include:

- Taste masking with flavours and sweeteners.
- Taste masking by polymer coating.
- Taste masking with ion-exchange resins.
- Taste masking by formation of inclusion complexes with cyclodextrins.
- Miscellaneous Taste-masking approaches.

Marketed Products Available As Fdt[23]

Table. 2. Commercially available Mouth disintegrating tablets.

Brand name	Active ingredient	Company
Zomig ZMT and Rapimelt	Zolmitriptan	AstraZeneca
Alavert	Loratidine	Wyeth Consumer Healthcare
Cibalginadue FAST	Ibuprofen	Novartis Consumer Health
Hyoscyamine Sulfate FDT	Hyoscyamine Sulfate	ETHEX corporation

MATERIALS

Acamprosate calcium Microcrystalline cellulose, Solutab, Polyplasdone XL, Magnesium stearate, Talc.

METHODS

Preparation of co processed super disintegrates

Co processed super disintegrates were prepared by using polyplastadone XL and Solutab. Weighed required amount of the super disintegrates were mixed then add methanol to obtained slurry, keep aside for evaporation to get a dried powder and sieve it and labeled as CP1, CP2, CP3, CP4, CP5. The coprocessed blend was used for preparing formulations of mouth dissolving tablets.

Table 3: Composition of co processed super disintegrates.

Ingredients	CP1	CP2	CP3	CP4	CP5
Solutab(mg)	500	500	500	1500	1000
Polyplasdone XL (mg)	500	1000	1500	500	500

Preparation of tablets

Composition of Acamprosate calcium Dispersible Tablet by direct compression is shown in table 4. All the ingredients were weighed. Required quantity of drug and excipient mixed thoroughly in a polybag. The blend is compressed using rotary tablet machine-10 station with 10mm flat punch, B tooling. Each tablet contains 50 mg Acamprosate calcium and other pharmaceutical ingredients.

Table: 4 Composition of various tablet formulations.

Ingredients	F1	F2	F3	F4	F5	F6	F7	F8	F9	F10
Acamprosate Calcium (mg)	300	300	300	300	300	300	300	300	300	300
CP 1(mg)	20	-	-	-	-	40	-	-	-	-
CP 2(mg)	-	20	-	-	-	-	40	-	-	-
CP 3 (mg)	-	-	20	-	-	-	-	40	-	-
CP 4 (mg)	-	-	-	20	-	-	-	-	40	-
CP 5(mg)	-	-	-	-	20	-	-	-	-	40
Mg Stearate (mg)	4	4	4	4	4	4	4	4	4	4
Talc (mg)	4	4	4	4	4	4	4	4	4	4
MCC (mg)	Qs	Qs	Qs	Qs	Qs	Qs	Qs	Qs	Qs	Qs
Total wt (mg)	400	400	400	400	400	400	400	400	400	400

Preformulation Studies

The goals of the preformulation study are:

- ❖ To establish the necessary physicochemical characteristics of a new drug substance.
- ❖ To establish its compatibility with different excipients.

Flow properties by Angle of Repose, Bulk Density (BD), Tapped density (TD), Carr's consolidation index, Hausner's ratio

Post Compression Parameters

Thickness, Hardness test, Friability test, Weight variation test, Drug Content estimation:

In -vitro dissolution studies

METHOD

Dissolution test was carried out by using USP type II apparatus. The paddle was rotated at 50 rpm. pH 6.8 phosphate buffer was used as dissolution medium (900ml) and was maintained at 37 ± 10°C. Samples of 5ml were withdrawn at predetermined intervals (5, 10, 15, 20 and 30), filtered and replaced with 5ml of fresh dissolution medium.

The collected samples were suitably diluted with dissolution fluid, where ever necessary and were analyzed for the drug at respective wavelength by using UV spectrophotometer. Each dissolution study was performed for three times and mean values were taken.

RESULTS AND DISCUSSION

Standard Calibration Curve Of Acamprosate Calcium:

It was found that the estimation of Acamprosate calcium by UV spectrophotometric method at λ_{max} 219.0 nm in pH 6.8 phosphate buffer had good reproducibility and this method was used in the study. The correlation coefficient for the standard curve was found to be closer to 1, at the concentration range, 5- 25µg/ml.

Table 5: Concentration and absorbance obtained for calibration curve of Acamprosate calcium in pH 6.8 phosphate buffer.

Concentration (µg/mL)	Absorbance* (at 219 nm)
0	0
5	0.107
10	0.212
15	0.32
20	0.41
25	0.51

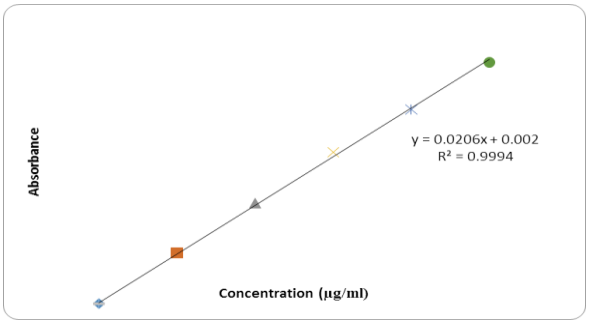

Fig 2: Standard graph of Acamprosate calcium in pH 6.8 phosphate buffer Drug And Excipient Compatability Studies.

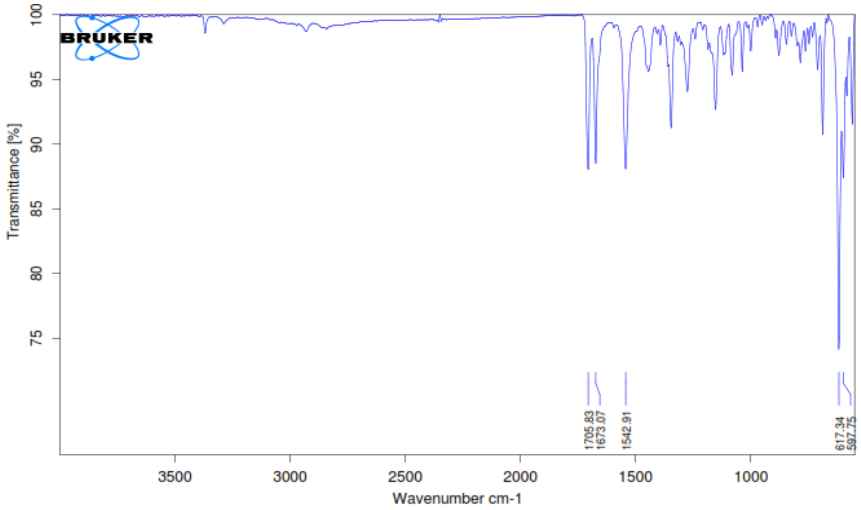

Figure: 3 FTIR of pure drug of Acamprosate calcium.

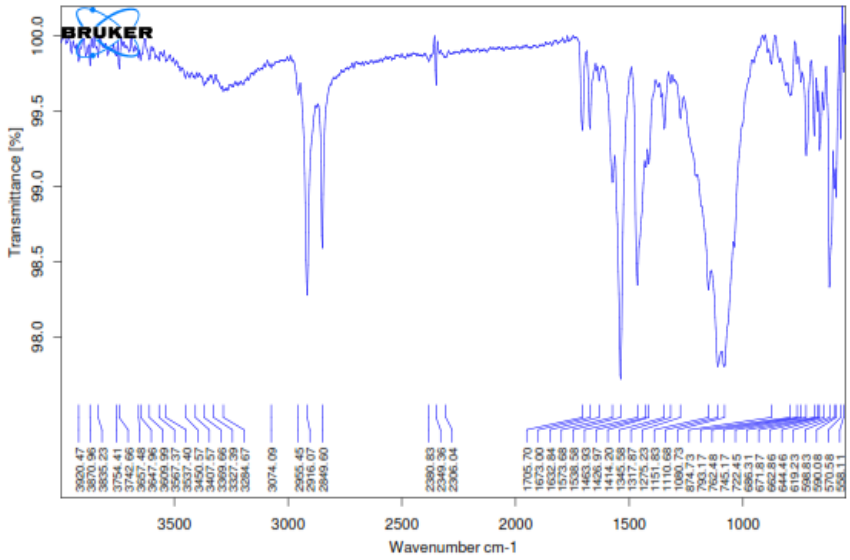

Figure: 4 FTIR of optimised formulation.

From the FTIR data it was evident that the drug and super disintegrates, other excipients doses not have any interactions**.** Hence they were compatible.

Evaluation Parameters For Fast Dissolving Tablets Of Acamprosate Calcium

Pre-compression parameters

The data's were shown in Table 6.The values for angle of repose were found in the range of 25°-30°. Bulk densities and tapped densities of various formulations were found to be in the range of 0.45 to 0.50 (gm/cc) and 0.52to 0.59 (gm/cc) respectively. Carr's index of the prepared blends was fall below 18. The Hausner ratio was fall below 1.2. From the result it was concluded that the powder blends had good flow properties and these can be used for tablet manufacture.

Table: 6. Pre compression parameters of formulation blend.

Formulation code	Angle of repose	Bulk density	Tapped density	Cars index	Hausners ratio
F1	25.91	0.45	0.53	15.04	1.17
F2	27.23	0.47	0.55	14.54	1.17
F3	26.34	0.50	0.58	13.79	1.16
F4	28.71	0.46	0.55	16.36	1.19
F5	29.34	0.50	0.58	13.79	1.16
F6	27.23	0.47	0.55	14.54	1.17
F7	28.34	0.50	0.59	15.25	1.18
F8	27.78	0.46	0.53	13.20	1.15
F9	29.78	0.47	0.52	14.89	1.10
F10	26.71	0.46	0.55	16.36	1.19

Table: 7 Post compression parameters for Fast dissolving tablets of Acamprosate calcium.

Formulation code	Average Weight (mg)	Thickness (mm)	Hardness (kg/cm^2)	Friability (%)	In-vitro disintegration time (sec)	Drug Content (%)
F1	400.01	4.69	4.5	0.63	22.33	99.23
F2	399.32	4.19	4.4	0.58	27.55	99.55
F3	400.4	4.82	4.5	0.59	20.33	100.16
F4	400.1	4.48	4.6	0.63	24.00	99.34
F5	399.4	4.90	4.5	0.59	17.33	98.16
F6	398.5	4.94	4.4	0.64	15.26	99.55
F7	399.6	4.69	4.5	0.55	21.33	101.16
F8	400.7	4.96	4.4	0.64	16.00	99.25
F9	399.9	4.44	4.5	0.64	14.00	98.57
F10	402.7	4.79	4.5	0.61	13.15	99.55

In vitro Dissolution studies

In vitro dissolution studies were carried out by using 900ml of pH 6.8 phosphate buffer in USP dissolution apparatus by using paddle method. The dissolution studies were carried out for about 60 min. The dissolution data for all the formulations were given in the Table 8.

Table 8: In vitro dissolution data.

Time (Min)	F1	F2	F3	F4	F5	F6	F7	F8	F9	F10
0	0	0	0	0	0	0	0	0	0	0
5	24.45	19.07	17.8	25.3	43	34.91	33.16	45.23	49.48	50.63
10	38.97	23.75	24.72	47.6	66.3	46.45	41.03	61.57	69.33	73.41
15	41.28	40.46	33.33	56.3	75.2	59.23	53.15	73.61	80.56	99.46
20	51.53	50.25	42.58	67.3	89.8	72.34	66.28	89.21	99.31	--
30	72.04	67.1	52.05	80.3	99.46	85.73	79.72	99.46		
45	87.1	79.3	69.47	95.1		99.47	87.43			
60	98.6	90.34	82.34	95.7			99.75			

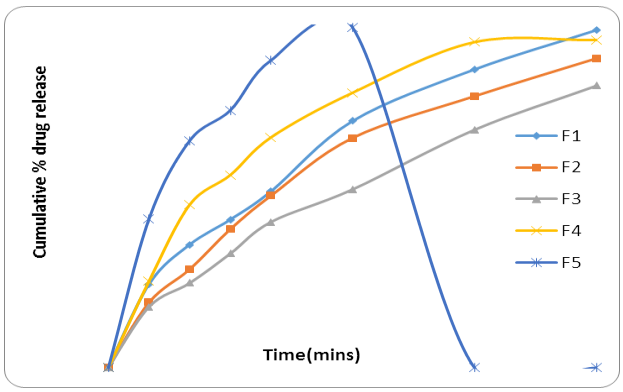

Fig 5: Dissolution profile of formulations prepared with 20mg of coprocessed blend.

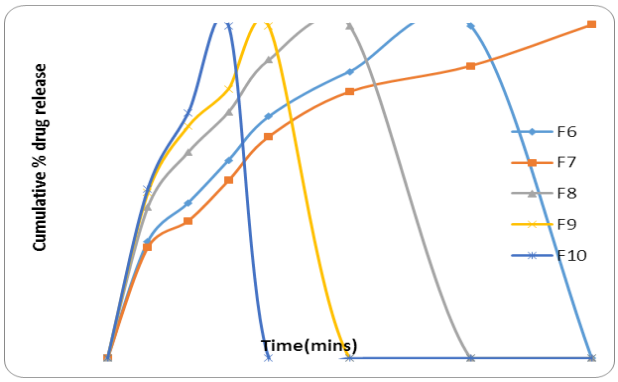

Fig 6: Dissolution profile of formulations prepared with 40 mg of coprocessed blend.

From the tabular column 4 it was evident that the formulations prepared with different concentration of coprocessed super disintegrate CP1, CP2, CP3, CP4 and CP5. Formulation F1-F5 was containing 20mg of Coprocessed blend (CP1 to CP5). Among five formulations F5 was showed maximum % drug release in 30 min i.e. 99.46 ± 1.58%.

Formulation F6-F10 containing 40 mg of coprocessed blend (CP1 to CP5) in that F10 formulation containing 40mg of CP5 showed maximum % drug release in 15 mins i.e 99.46 ± 1.47%.

Among all the ten formulations F10 containing 40 mg of CP5 showed maximum drug release in within 15 mins due to less disintegration time. So F10 formulation was considered as optimised formula.

CONCLUSION

The present study was carried out on Acamprosate Calcium Fast dissolving tablets using coprocessed method. In this study coprocessd agents were Polyplasdone XL and Solutab and remaining exciepients Magnisium stearate, Talc and Micro crystalline cellulose were also used. Those all ingredients weighed and blended properly and compressed directly using rotary tablet compression machine (mfg by Lab Press).

The pre and post compression studies like bulk density, tapped density, carr's index, hausner's ratio, angle of

repose and weight variation, thickness, hardness, friability, drug content were found to be within limits. In vitro drug release studies were revealed that Among all formulations F10 formulation shown optimum drug release.

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