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Orodispersible - Slow Releasing Erythromycin Tablets

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Abstract: The purpose of the present research was to study the effect by using variable quantity of orally ingestible excipients such as amino acids like Isoleucine, Arginine on the oral dispersible property of Erythromycin tablets and to evaluate loading of different hypromellose grades containing Methocel K4M and Methocel 100 KM which were used as sustained release agents for pediatric, mentally ill and uncooperative patients by the use of meltable binders which disperse in mouth at body temperature. Six formulations were developed with drug (45%), lipophillic meltable binders (9.7%), Sustained Release (SR) materials (25%), orally ingestible material i.e. amino acids(5%) by altering the excipients i.e. SR agents and amino acids respectively. The tablets were evaluated for weight variation, hardness, friability, wetting time, water absorption ratio, disintegration time and dissolution study. An optimum release was found in formulation with F5 and F6, HPMC K100M was more viscous and less erodible than that of HPMC K4M providing a stronger barrier for drug diffusion and resulting in a slower drug release rate (12hrs). Through DSC studies it can be concluded that the granules showed absence of interactions between the components. These results suggest that melt granulation could be an easy and fast method to formulate sustained release, oro-dispersible tablets of Erythromycin.
Key words: Oral ingestible excipients, microcrystalline cellulose, croscarmellose sodium, sodium lauryl sulphate, Isoleucine, Arginine.

1. INTRODUCTION

Orodispersible tablet is a dosage form that is to be placed in the mouth where it disperses rapidly before swallowing. The presence of a super-disaggregant makes it possible to produce sufficiently hard tablets that still disaggregate within seconds and most of the developed tablets can be considered as ‘‘fast dispersible”. In the present study an attempt was made to program the formulation not only for oral dispersibility, but also for delayed release, with dissolution of the drug taking place far from the buccal and gastric environment[1].

In the recent past, several new advanced technologies have been introduced for the formulation of orodispersible tablets with very interesting features, like extremely low disintegration time, exceptional taste masking ability, pleasant mouth feel and sugar free tablets for diabetic patients[2]. The technologies utilized for fabrication of orodispersible tablets include lyophilization[3], moulding[4], direct compression[5], cotton candy process[6], spray drying[7], sublimation[8], mass extrusion[9], nanonization and quick dissolve film formation[10]. These techniques are based on the principles of increasing porosity and/or addition of superdisintegrants and water soluble excipients in the tablets[11]. The formulations prepared from these techniques differ from each other on the basis of the factors like mechanical strength of final product, drug and dosage form stability, mouth feel, taste, rate of dissolution of the formulation in saliva, rate of absorption from saliva and overall drug bioavailability and polymers[12].

A newer and easier technique adapted for the formulation of orodispersible with sustained release of medicament from the tablet dosage form could be the melt granulation technique[13].

Erythromycin 9-{O-[(2-methoxyethoxy) methyl] oxime} is a macrolide antibiotic which prevents bacteria from producing proteins, which hinders the bacterial growth and multiplication, while not affecting human cells. It is used In the in the treatment of wide variety of infections like bronchitis, severe campylobacter enteritis, chancroid, diphtheria, legionnaires, pneumonia sinusitis and trench fever[13]. In this present study, an attempt was made to develop orally dispersible tablets using orally ingestible excipients and to investigate the effect of hypromellose grades polymers on the sustained release pattern of the drug . Erythromycin has better absorption characteristics in the small intestine than in the stomach, and has a half-life of 1 to1.5 hrs, hence an enteric coating is preferably applied to the erythromycin granules for sustained release of the drug from the dosage form. This enhances the safety and efficacy of drug molecule and provide ease of administration for those who refuse to swallow, such as, pedriatric, mentally ill and uncooperative patients[14]. In this present study, the immediate release formulations were achieved by hot melt technology that facilitates and enhances the excipients' solubility with palatability and disperses faster at mouth, and provide sustained release in small intestine by using novel polymers such as hypromellose grades.

2. MATERIALS AND METHODS

2.1. Materials

Erythromycin, amino acids and hypromellose grade polymers was obtained as a gift sample from Ace Rasaya from Mysore, Karnataka. All other chemicals used in the study were of analytical grade.

2.2. Methods

Preparation of Erythromycin Pellets

The granulation procedure was standardized on the basis of preliminary trials. The mixture composed of Erythromycin (50%), HPMC (Methocel K4M Premium and Methocel K100M) (30 %) in polymer solution of acrycoat L30D in propylene glycol and a binding agent (20%) were mixed at an impeller speed of 250 rpm for 5-10 min. Successively the mixture was heated with the heating jacket up to the melting point of the binder and the impeller speed was increased in order to obtain granules. At the end of the granulation process the granules were cooled at room temperature by decreasing the jacket temperature to 25ºC and tilting the bowl the pellets were prepared.

Preparation of Orodispersible Sustained Release Erythromycin Tablets

Six Erythromycin formulations were developed (table 1). Physical mixtures of Erythromycin sustained release pellets and polyethylene glycol 1500 were heated to liquid at 78ºC. After solidification, the mixtures were pulverized and sieved through 30 mesh screens. The hot melt product was granulated with amino acid(s) and guar gum. The granulated hot melt product was then blended with microcrystalline cellulose, croscarmellose sodium, and sodium lauryl sulphate. The final blends were compressed into tablets with a Carver press using Natoli HOB #67146 modified oval tooling. The compaction force was 4000 pounds. Six formulation with varied proportion of oral ingestible excipients such as amino acids like Isoleucine, Arginine and with both of amino acids were prepared and compared.

3. EVALUATION OF ERYTHROMYCIN TABLETS

3.1 Weight variation

Twenty tablets were selected at a random and average weight was calculated. Then individual tablets were weighed and the individual weight was compared with an average weight. The results are shown in table 2.

3.2 Hardness and Friability

Tablets were evaluated for hardness and friability test using Monsanto hardness tester and Roche friabilator respectively. The results are shown in table 2.

3.3 Wetting Time and water absorption ratio

Wetting time and water absorption ratio is intimately related to the hydrophilicity of the excipient and to the pore size of tablets. A piece of tissue paper folded twice was placed in a small Petri-dish (internal diameter of 5 cm) containing 6 ml of water. A tablet was placed on the paper and the time required for complete wetting was measured. The wetted tablet was then weighed The results are shown in Table 2. Water absorption ratio 'R' was determined using the equation,

$R=100\{(W_a - W_b) / W_b\}$

where W_a is weight of tablet before water absorption and

W_b is weight of tablet after water absorption.

3.4 Invitro disintegration time

In vitro disintegration time was measured by dropping a tablet in a beaker containing 50 ml of Sorenson's buffer pH 6.8. Three tablets from each formulation were randomly selected and in vitro dispersion time was performed and time in seconds taken for complete disintegration of the tablet with no palatable mass remaining in the apparatus was measured (table 2).

Table 1: Development of Oro-dispersible tablets

Ingredients (in mg)	F1	F2	F3	F4	F5	F6
Erythromycin	225.5	225.5	225.5	225.5	225.5	225.5
Methocel K4 M	125	---	125	---	125	---
MethocelK100M	---	125	---	125	---	125
PEG 6000*	15.5	15.5	15.5	15.5	15.5	15.5
Stearic acid: Gleyceryl Monosterare*	23/10	23/10	23/10	23/10	23/10	23/10
Acrycoat L30	37.5	37.5	37.5	37.5	37.5	37.5
Guar cum	15	15	15	15	15	15
Isoleucine	25	25			25	25
Arginine			25	25	12.5	12.5
Lactose	30.5	30.5	30.5	30.5	12.5	12.5
Ac- Di- sol	20	20	20	20		
SLS	11.5	11.5	11.5	11.5	11.5	11.5
Talc	10	10	10	10	10	10
Total(in mg)	500	500	500	500	500	500

(*indicates meltable binders whose weight gets reduced with heating)

Table.2: Evaluation of oral dispersible tablets

Formulation	Weight variation	Hardness test (kg/cm^2)	Friability test	Wetting time (sec)	Water absorption ratio	Invitro disintegration time	Drug release study
F1	507±0.002	3.87	0.88±0.01	42.03±1.08	79±0.223	45.84±1.36	86.41
F2	509±0.011	3.67	0.91±0.01	43.41±0.59	80±0.11	43.8±0.9	77.01
F3	511±0.003	3.55	0.78±0.02	35.23±0.51	88±0.32	37.98±0.66	91.98
F4	502±0.002	3.93	0.98±0.1	36.02±1.02	86±0.41	38.54±0.09	80.76
F5	508±0.004	3.79	0.85±0.14	34.47±0.98	72±0.9	35.24±0.96	94.58
F6	507±0.03	3.82	0.86±0.02	33.21±0.4	77±0.621	34.12±0.51	83.41

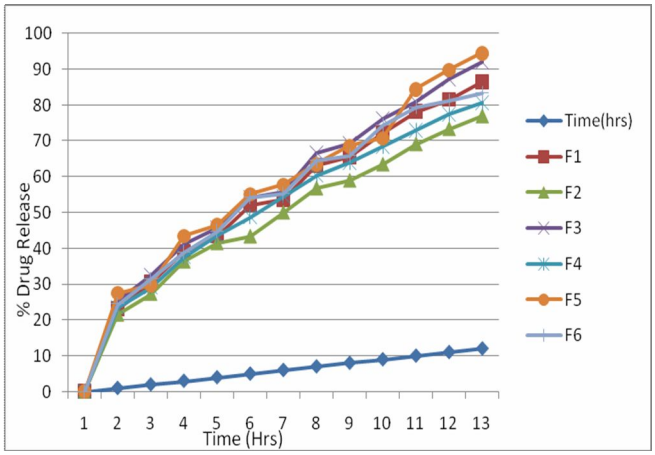
3.5 Dissolution Studies

In vitro drug release studies of all the formulations were carried out using tablet dissolution test apparatus Dissolution studies were conducted by Type II USP apparatus at 100 rpm in 900 ml of simulated gastric fluid TS (prepared without pepsin) for 1 hour. Then granules were placed in 900 ml phosphate buffer pH 6.8. The dissolution medium was kept under stirring at 100 rpm. All the experiments were carried out at 37 ^{0}C for 1 h. at 37.0±0.5ºC. The release of Erythromycin was detected at UV 290 nm. Predetermined time intervals and an equivalent amount of fresh dissolution fluid equilibrated at the same temperature was replaced. Samples were analysed using UV-Visible spectrophotometer (table 3)**.** The sample after each withdrawal was replaced with same volume of fresh media and the test was conducted in triplicate.

Table 3: Drug release profile of erythromycin oral dispersible tablets

Time(hrs)	F1	F2	F3	F4	F5	F6
0	0	0	0	0	0	0
1	23.02	21.58	25.32	23.58	27.58	24.49
2	30.42	27.38	32.48	29.07	29.85	31.52
3	39.12	36.41	41.28	37.55	43.48	39.01
4	43.41	41.51	45.68	43.56	46.51	44.83
5	52.1	43.41	54.25	48.81	55.13	54.3
6	53.58	50.09	55.84	54.56	57.81	55.41
7	63.13	56.86	66.62	60.37	63.54	64.59
8	65.41	59.01	69.17	63.95	68.56	65.98
9	72.08	63.51	76.13	68.48	70.79	74.41
10	78.08	69.19	80.79	73.05	84.41	79.56
11	81.44	73.41	87.22	77.57	89.93	81.16
12	86.41	77.01	91.98	80.76	94.58	83.41

Fig. 1: Graph representing % drug release at 6.8 pH for 12hrs.



3.6 FTIR Evaluation

This method of analysis was used to examine and compare the structural changes that might result when granulation was done. The IR patterns of granules were compared with that of each component. Samples of Erythromycin, Acrypol 934P, and granules were crushed differently with KBr to make KBr pellets. Their IR spectra were recorded over the region 400 to 4000 cm^{-1}. IR spectra of test samples are given in Fig 2.

3.7 Differential Scanning Calorimetry (DSC)

The DSC analyses were performed using a DSC-50 calorimeter/TAC-50 (Shimadzu Corp.,
Kyoto, Japan). Samples of about 5 mg were sealed in a 30 µl aluminium pan and were scanned between 10ºC and 300ºC at a heating rate of 10ºC/min. DSC studies of test sample are given in Fig 3.

Fig. 2: IR evaluation of Erythromycin, excipeints and interaction

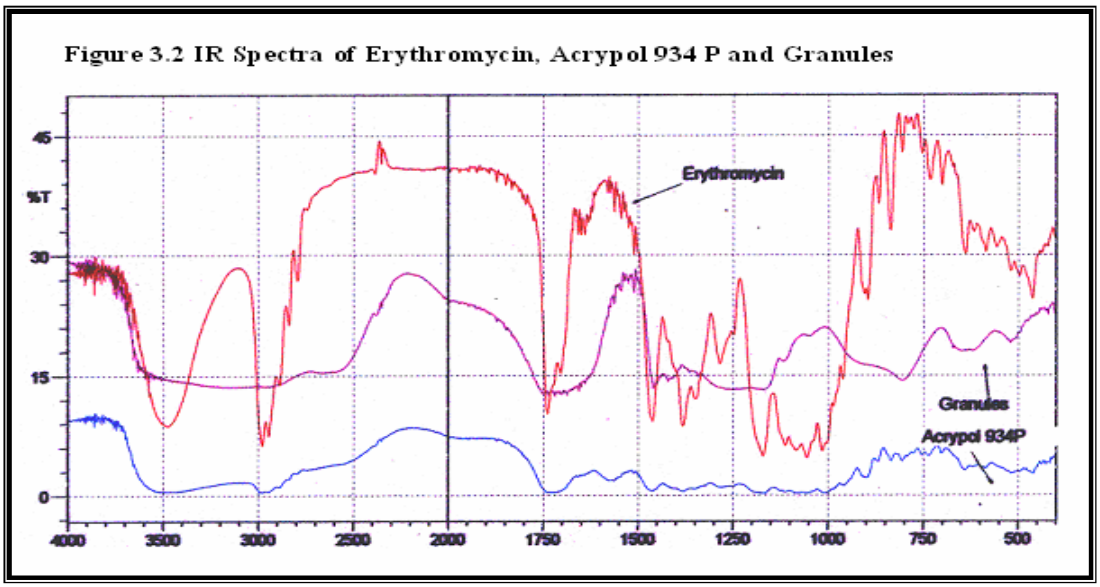
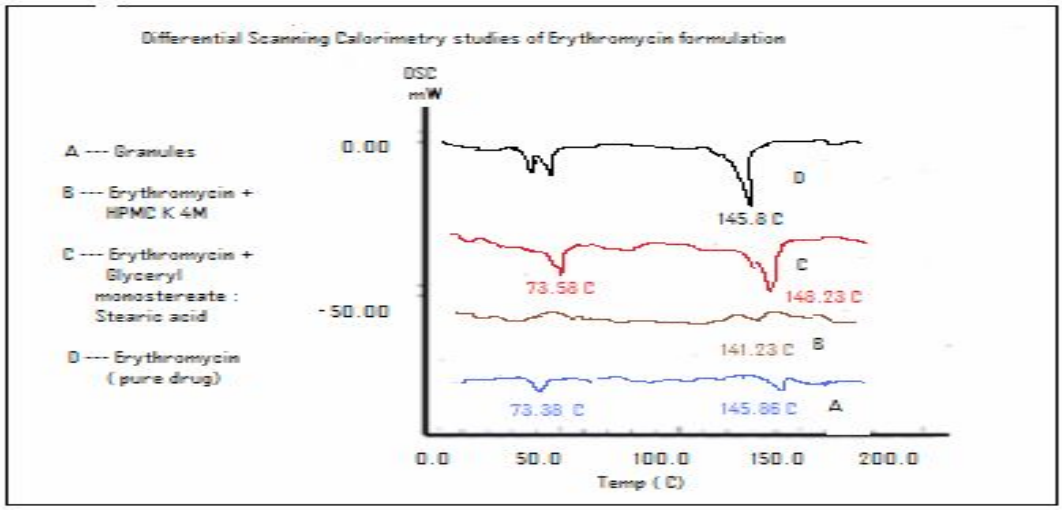


Fig. 3: Diffrential scanning calorimetric studies



4. RESULTS AND DISCUSSION

4.1 FTIR evaluation:

The granule is believed to be held together by interactions such as (i) the ionic attraction between the amino sugar group of erythromycin and the carbonyl group of the carbomer, and (ii) the gel properties of the carbomer. Overlapped FT IR spectra of Erythromycin, Acrypol 934 P and granules (with HPMC grades) are depicted in Figure 2. The drug showed a strong band at 2850–2250 cm^{-1} due to the stretch of the tertiary amine, but only appeared as a weak band in the interaction product. The disappearance of the strong band at 2850–2250 cm^{-1} suggests the nonexistence of free 3^{o} amine group, while the appearance of the weak band suggests the formation of a salt between the high molecular weight acidic polymer and the relatively small molecules of the drug i.e ''O'' of ''COO'' and polymer with that of ''N'' atom of drug.

4.2 Differential Scanning Calorimetry

The DSC curves were obtained for erythromycin, excipients, their physical mixture with the same proportion of the tablets, and granules obtained by melt granulation. The DSC analysis of erythromycin showed a single endothermic peak at 145 ± 2ºC, due to the melting of the drug. HPMC K4M and K100M did not show any characteristic peak, and binder agents showed their respective peak at their melting range (Glycerol monostearate: 55-60ºC, Stearic acid: 55-60ºC and PEG 6000: 55-63ºC). In the DSC curves of physical mixtures and melt granules the characteristic peaks of Erythromycin and binder agents were almost unchanged indicating the absence of strong interactions between the components and suggesting drug-excipient compatibility in all the formulations examined.

4.3 Dissolution studies

Different release behaviours depending on the binders used in preparation which is evaluated by *In-vitro* dissolution results shows that the matrices prepared with granules obtained by melt granulation provided a sustained release of the drug. Formulations prepared with lipophilic binders (such as Stearic acid and Glycerol monostearate) showed the slowest release rate and their dissolution profiles were almost super imposable. Only after 12 hrs around 80-95% of the total drug amount was released for both HPMC K4M and K100M celluloses. On comparison for the formulations containing PEG 6000 and HPMC K4M, the later achieved the total release of the drug at 12 hrs, whereas the formulation with PEG 6000 and HPMC K100M only released around 80% (fig. 1). Differences between cellulose grades can be explained by the fact that the gel layer of HPMC K100M was more viscous and less erodible than that of HPMC K4M, providing a stronger barrier for drug diffusion, and resulting in a slower drug release rate (12hrs).

5. CONCLUSION

The results suggest that melt granulation could be an easy and fast method to formulate sustained release tablets. Hot melt technology, especially when combined with specific amino acid(s) significantly increased the dispersion of Erythromycin in the oral cavity. Formulation (F5) containing Methocel K4M showed sustained drug release for over 12hrs, emerging as best formulation.

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