Available online at www.pharmacie-globale.info ISSN 0976-8157

Research Article

PHARMACIE GLOBALE

INTERNATIONAL JOURNAL OF COMPREHENSIVE PHARMACY

FAST DISSOLVING ROXITHROMYCIN TABLETS CONTAINING SOLID DISPERSION OF ROXITHROMYCIN

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Received: 21 June 2011; Revised: 22 August 2011; Accepted: 29 August 2011; Available online: 5 September 2011

ABSTRACT

Roxithromycin, is one of the macrolid antibiotics for respiratory infections.It is slightly soluble in water, hence present study was carried out to enhance dissolution properties of Roxithromycin. Through the preparation of Solid Dispersions using Mannitol as carrier at various proportions (1:1,1:2,&1:4) by using different techniques like Physical mixtures, Melt Solvent and Melting method. The drug release profile was studied in 900ml of distilled water. UV Spectrophotometer method was selected for assay as well as *in-vitro* dissolution studies at 203 nm. The dispersions were evaluated for drug content uniformity, dissolution rate study; DE_{20}, T_{50}.The FTIR and DSC were used to characterize the solid state of solid dispersions. A marked increase in dissolution rate was observed with all solid dispersions among that the optimized solid dispersion was selected for tablet formulation.

Keywords: Roxithromycin, Solid dispersion, Physical mixtures, Melt Solvent method, Melting method and Commercial formulation.

INTRODUCTION

Roxithromycin[1], is one of the macrolid antibiotics for respiratory infections. It is slightly soluble in water, hence present study was carried out to enhance dissolution properties of Roxithromycin. The rate of dissolution can be increased by increasing the surface area of available drug by various methods like Micronization, Complexation and Solid dispersion (SD).[2] Hence, an attempt was made to improve the dissolution characteristics using the solid dispersion technologies. Among various approaches to improve the dissolution rate of poorly soluble drugs, the preparation of solid dispersions has often proved to be successful[3-7], nifedipine[8], meloxicam[9], lansoprazole[10], valdecoxib[11], aceclofenac[12], carbamazepine[13], glimipiride[14], etoricoxib[15] various hydrophilic carries such as poly ethylene glycols[16], polyvinyl pyrrolidone[17], sugars[18], urea[19] have been investigated for improvement of dissolution characteristics and bioavailability of poorly aqueous soluble drugs. In the present work, solid dispersions of Roxithromycin with Mannito[20,21] prepared in different drug : carrier ratios (1:1, 1:2 & 1:4,) with different techniques like physical mixing (PM), Melt solvent (MS) and Melt method (MM) to improve solubility and dissolution characteristics. UV Spectrophotometric method[22] was selected for assay as well as *in-vitro* dissolution studies at 203 nm in 900 ml distilled water. The dissolution profile of best formulation i.e. Drug: Mannitol (1:4) melt method showed maximum dissolution rate which was selected for formulation of tablets containing 10% Starch and MCC. The increase in dissolution rate of the drug may be due to increased wettability, hydrophilic nature of the carrier and also possibility due to reduction in drug crystallinity.

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MATERIALS AND METHODS

Roxithromycin was procured from Acto Pharmaceuticals private limited, Warangal, Mannitol purchased from Qualigens fine chemicals Mumbai, Microcrystalline cellulose and Magnesium stearate purchased from S. D fine chemicals Ltd. Mumbai all other materials used were of pharmaceutical grade.

Preparation of physical mixture

Accurately weighed quantities of roxithromycin and mannitol in the ratios of. (1:1, 1:2 and 1:4) were taken in a glass mortar and were mixed thoroughly. The resultant mixture was passed through sieve no: 100 and stored in a dessicator.

Preparation of solid dispersion

Melt solvent method: Reqquired quantity of mannitol was taken in a china dish and melted on a water bath. Then accurately weighed quantity of roxithromycin was taken and dissolved in methanol. The prepared solution was poured in to the melt of mannitol at 165°C. The china dish was kept in an ice bath for sudden cooling. The solidified mass was scrapped, crushed, pulverized and passed through sieve no: 100 the obtained product was stored in a dessicator.

Melt method: Accurately weighed quantities of roxithromycin and mannitol in the ratios of. (1:1, 1:2 and 1:4) were taken in a glass mortar and were mixed thoroughly, then the physical mixtures were transferred in to a china dish and was melted on a sand bath, the fusion temperature was controlled between 160°C to 175°C. The

molten mixture was immediately cooled and solidified in an ice bath with vigorous stirring. The mass obtained was scrapped, crushed, pulverized and passed through sieve no: 100. The obtained product was stored in a dessicator.

Estimation of Roxithromycin

A quantity of solid dispersion equivalent to 100 mg of Roxithromycin was accurately weighed and dissolved in 0.1N HCl in 100ml. An ultraviolet (UV) Spectrophotometric method based on the measurement of absorbance at 203nm in 0.1 N HCl was developed and used for the estimation of Roxithromycin. The method obeyed Beer's law in the concentration range of 0-50 mcg/ml where concentration of standard solution was assayed repeatedly (n = 3).

Dissolution rate study

The dissolution rate of Roxithromycin as such and from its Solid Dispersions was studied using Disso 2000, Lab India 8-station Dissolution rate test apparatus with a paddle stirrer. The dissolution rate was studied in 900ml of distilled water. Roxithromycin (150 mg) or its solid dispersion equivalent to 150 mg of Roxithromycin, with speed of 50 rpm and temperature of 37±1°C were used in each test samples of dissolution medium (5 ml) were withdrawn through a filter (0.45 µ) at different time intervals, suitably diluted and assayed for Roxithromycin by measuring absorbance at 203 nm. The dissolution experiments were conducted in triplicate.

Formulation and preparation of tablets of Roxithromycin-mannitol solid dispersion

The tablet formulations F1, F2, F3 &F4, were developed from Roxithromycin-mannitol solid dispersion by wet granulation method. Among that F4 has shown maximum *in-vitro* dissolution, using 10% Starch and starch paste as binding agent and disintegrant. Aerosil (1%) and magnesium stearate (1%) were used as a glidant-lubricant. The average weight of the tablet was adjusted to 850 mg using micro-crystalline cellulose as diluents. The required quantity of SD was taken in to a mortar to this add half quantity of starch powder then mixed throughly by adding starch paste drop wise until a wet mass was formed. The wet mass passed through sieve no: 10. The formed granules were dried at 40°C. The dried granules once again passed through sieve no: 16. To these granules the remaining half portion of starch powder, Aersoil (1%) and magnesium stearate (1%) were added and mixed throughly. These granules were compressed into tablets (850mg weight) on a Rimek rotary tablet machine (Karnavati Eng. Pvt. Ltd, Ahemedabad). The Tablets were stored in a tightly closed glass container and evaluated for physical characteristics in triplicate.

Evaluatin of the tablets of Roxithromycin-mannitol solid dispersions

Compressed tablets were then evaluated for hardness[23], disintegration[24], Friability[25] and drug content. Hardness was measured by Monsanto type hardness tester. One tablet was placed in each tube of disintegration apparatus (USP/IP standard). The test was carried out using distilled water as a disintegration media at 24°C±2°C. Friability was determined in friabilator (model Ef- 2, electro lab), by taking 10 tablets. For drug content analysis 20 tablets were accurately weighed and finely powdered. The quantity of powder equivalent to 100 mg of Roxithromycin was taken into a 100ml volumetric flask and volume adjusted to 100 ml with 0.1N HCL and filtered. Filtrate was diluted suitably and assayed for drug content at 203nm. Using double beam UV-visible spectrophotometer (Shimadzu, model -1700). The drug content of the tablet was found to be 100.2%.

***In-vitro* dissolution study of tablets**

In-vitro dissolution study of the tablets[26,27] was conducted using USP dissolution. Apparatus-2, at 50 rpm using distilled water as a dissolution media at 37°C±0.5°C. Samples were withdrawn at various time intervals. Filtered through a 0.45 micron membrane filter, diluted, and assayed at 203nm using UV-visible double beam spectrophotometer.

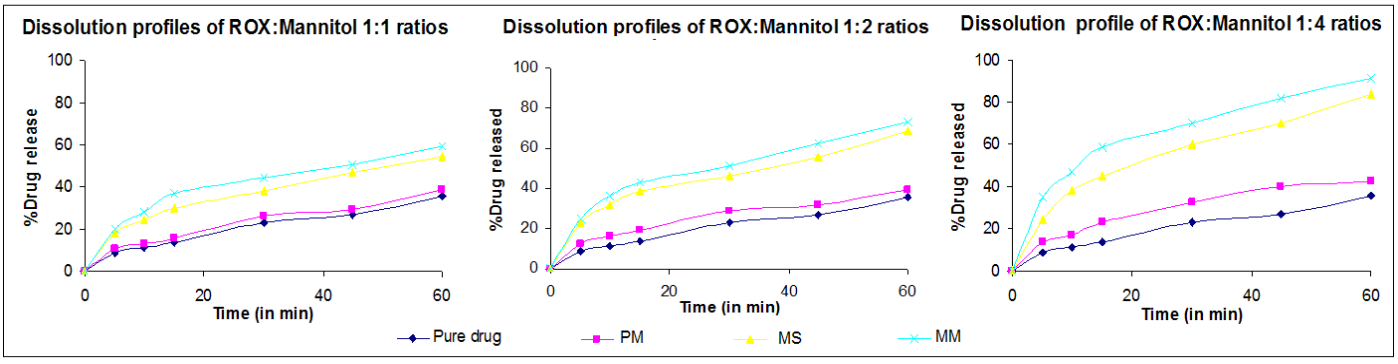
Stabilitsty study of F4

In order to determine any change in *in-vitro* drug release profile on storage. Stability of F4 was carried out at 40°C and 75%RH in stability chamber [Thermolab]. The formulation was withdrawn after 4 weeks and evaluated for change in *in-vitro* drug release pattern, hardness and disintegration time.

RESULTS AND DISCUSSION

All the Solid dispersions(SD_S) was found to be free flowing. Low values of C.V (<1.0%) in percent drug content indicated uniformity of drug content in each batch of solid dispersions. The dissolution profiles of various physical mixtures and sold dispersions were shown in Figure **1**.

Figure 1. Dissolution profiles of roxithromycin from mannitol solid mixtures prepared by different methods



All the Physical mixtures and solid dispersions showed rapid dissolution of Roxithromycin as compared to pure drug. The dissolution rate of Roxithromycin Increases with Increase in Mannitol, up to 1:4 ratio of drug; mannitol this increase in dissolution rate may be due to improved wettability by the carrier. The dissolution rates of solid dispersions prepared by melt method were greater than the dissolution rates of solid dispersions prepared by other methods. The order of dissolution rates are MM>MS>PM>Pure drug. In each case the dissolution was found to obey First order kinetics(R>0.9924). The dissolution rate constant (K_1) was calculated from the slope of the first order linear plots of the dissolution data. The dissolution efficiency (DE_{20}) value based on the dissolution data were calculated according to Khan[28]. T_{50} (time taken for 50 % dissolution) values were recorded

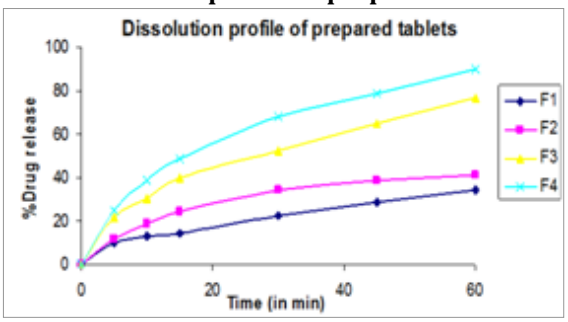
from the dissolution profile. The dissolution parameters of pure drug, PM and SDs were shown in Table **1.**

Table 1. Dissolutoin Parameters of Roxithromycin Solid Dispersions Prepared

Product	% Dissolution in 10 min	T_{50} min	DE_{20} (%)	K_1 (min^{-1})	r
Roxithromycin	-	>60	-	-	-
Physical Mixture (PM)					
1:1	12.50	22.16	12.25	0.00644	0.9639
1:2	16.10	15.56	15.01	0.00690	0.9370
1:4	18.50	13.26	19.78	0.00736	0.9705
Melt Solvent (MS)					
1:1	23.50	15.14	26.50	0.01151	0.9483
1:2	32.00	13.38	33.67	0.01658	0.9492
1:4	34.00	11.14	37.59	0.02533	0.9882
Melt Method (MM)					
1:1	26.50	11.50	29.14	0.01289	0.919
1:2	36.80	10.48	40.28	0.01911	0.9556
1:4	38.92	9.10	47.26	0.03454	0.9924

It is indicated that The Roxithromycin: mannitol 1:4. Melt method shown maximum dissolution rate. It was converted to cost effective tablet formulation with improved dissolution. F4 gave faster dissolution rate than the tablets prepared according to other formulae shown in Figure **2**.

Figure 2. Dissolution profile of prepared tablets



The mean hardness was 3kg/cm². The disintegration time was found to be 160s. The friability and assay of F4 was found to be 0.382% and 100.6% respectively**.** Figure **3** shows comparision between the *in-vitro* release profiles of F4 with conventional marketed tablet containing 150 mg of Roxithromycin. The results were similar to marketed tablet. F4 showed 89.98% in 60 min marketed product with 86.98% in 60min. The T_{50} and percentage dissolution efficiency (DE_{20}) values of prepared tablets and MP were shown in Table **2** and *in- vitro* drug release kinetic data of F4 and MP were shown in Table **3.**

Figure 3. Comparative *in-vitro* release profile of F4 and marketed formulation

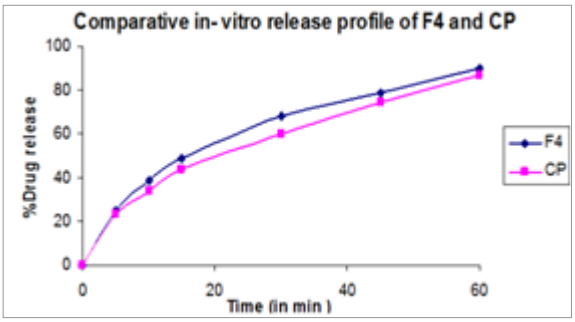


Table 2. Dissolution parameters of prepared tablets and commercial formulation

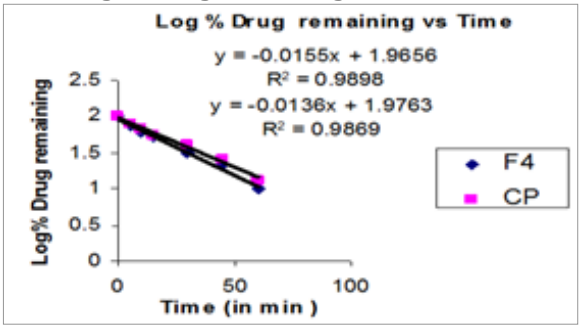
Formulation	DE20	T50
F1	11.71	17.50
F2	17.39	13.00
F3	36.64	11.50
F4	47.62	9.00
Commercial formulation	38.64	10.50

Table 3. *In-vitro* drug release kinetic data of commercial product and F4

Commercial formulation					Best formulation F4				
Zero order	Log% drug remained Vs Time		In(min)	(%)	Zero order	Log % drug remained Vs Time		In(min)	(%)
(r)	(r)	K_1	$t_{1/2}$	DE_{20}	(r)	(r)	K_1	$t_{1/2}$	DE_{20}
0.9226	0.9869	0.03132	22.126	38.64	0.0890	0.9898	0.03569	19.417	47.62

It is clearly evident that F4 and marketed product are greater than pure drug. So F4 as considered cost effective formulation with higher *in-vitro* dissolution. The dissolution was found to obey first order release in each case of F4 and MP respectively shown in Figure **4**.

Figure 4. Log % Drug remaining Vs Time



The obtained DSC thermogram corresponding to the melting point of roxithromycin and mannitol indicated that SDs was stable and absence of any additional peak indicated no interaction between drug and carrier. IR spectroscopy was used to study the possible interaction between roxithromycin and mannitol in SDs the spectra showed the characteristic peaks corresponding to the drug and carrier used was unchanged showing no significant interaction between drug and carrier. In order to determine the change in the *in-vitro* release profile on storage stability study of F4 was carried out at 40°c and 75% RH for one month, no visible physical changes were observed in the formulation withdrawn from the humidity chamber.

CONCLUSION

From the above investigations it was concluded that the solid dispersion technique could be successfully used to improve the water solubility of roxithromycin using mannitol as carrier**.** The tablets prepared from Roxithromycin: Mannitol 1:4 ratio prepared by Melt method containing 10% starch and MCC i.e. F4 shown high promising improvement in the dissolution characteristics and thus there is possible enhancement in the bioavailability of Roxithromycin.

ACKNOWLEDGMENT

The Authors are thankful to Acto Pharmaceuticals private limited, Warangal for providing the gift sample of Roxithromycin, and the Principle, Dr H L T College of Pharmacy, Channapatna, Ramanagra, Distt, Bangalore for providing the necessary facilities.

REFERENCES

1. Martindil: The complete drug reference, 33rd Ed, pharmaceutical press. 2002; 247.
2. Martin A, Editor, Physical pharmacy, 4th Ed, Philadelphia Lippin Cott Williams and Wilkins. 1993; 324-362.
3. Swarbrick and Baylan Encyclopedia of Pharmaceutical technology, Marcel Dekker Inc, Newyork. 2nd Ed, Vol 1, 2002; 641-647.
4. Leunnerc Dressman J; Improving drug solubility for oral delivery using solid dispersions. *Eur J Pharm Bio Pharm*. 2000; 50:47-60.
5. Brahmankar B M, Jaiswal S B; Biopharmaceutics and Pharmaceutics,1st Edition, Vallabh prakashan, Delhi. 1995; 297-302.
6. Chiou W L, Riegelman S; Preparation and dissolution characterization of several Fast release Solid Dispersions of Griseofulvin. *J Pharm Sci*. 1969; 58:1505-1510.
7. Chiou W L, Riegelman S; Pharmaceutical applications of Solid Dispersion Systems. *J Pharma Sci*. 1971; 60:1281-1302.
8. Vippagunta S R, Maul K A, Tallava Jhala S, Grant D J W; Solid state characterization of Nifedipine Solid dispersions. *Int J Pharm*. 2002; 236:111-123.
9. Malleshwar Rao V S N, Shyam T, Appa Rao B, Srinivas Rao; Formulation and Characterization of Meloxicam Solid Dispersions. Indian Pharmacist. 2008; 7(70):67-70.
10. Mamatha T, Venkateshwar Rao, Mallik B, Shagufta Ahmed and Shanti M; Studies to Enhance Dissolution of Lansoprazole. The Indian Pharmacist. 2008; 7(74):65-70.
11. Patel M M, Patel D M; Fast Dissolving Valdecoxib Tablets containing Solid Dispersions of Valdecoxib. IJPS. 2006; 68:222-226.
12. Kamal Dua, Ramana M V, Sara U V S, Himaja M, Garg V, Agarwal A, Mehta D; Dissolution Enhancement of Aceclofenac through Solid Dispersions. The Indian Pharmacist. 2002; 6:70-72.
13. Prajapati S T, Gohel M C, Patel L D; Studies to Enhance Dissolution Properties of Carbamazepine. IJPS. 2007; 69:427-430.
14. Srinivas P B, Ramu A, Shashidhar, Vidyadhara; Enhancement of Dissolution rate of Glimepiride using newer carriers. The Indian Pharmacist. 2008; 7(69):65-68.
15. Bhanubhai N, Suhagia, Patel H M, Shailesh A, Rathod I S, Parmar V K; Preparation and Characterization of Etoricoxib- Polyehtylene Glycol 4000 plus Polyvinyl pyrrolidone k-30 Solid Dispersions. *Acta Pharm*. 2006; 56:285-298.
16. Liu C, Desai K G; Chjaracterization of Rofecoxib-PEG 4000 Solid Dispersions and tablets based on Solid Disoersions. *Pharma Dev Technol*. 2005; 10:467-477.
17. Sethi S, Squllante E; Solid Dispersions of Carbamazepine in PVPK-30 by conventional solvent evaporation and supercritical methods. *Int J Pharma*. 2004; 19:1-10.
18. Loyd V, Allen Jr, Levinson R S, Martono D D; Dissolution rates of Hydrocartisone and Prednisone utilizing sugars Solid Dispersion systems in tablet form. *J Pharma Sci*. 2006; 67:979-981.
19. Chiou W L, Niazio S; Phase diagram and dissolution rate studies on sulpha thiazole-urea solid dispersions. *J Pharma Sci*. 2006: 60:1333-1338.
20. Raymond C Rowe, Paul j Sheskey and Paul J Waller. Hand book of harmaceutical Excipients, 4th Ed. The pharmaceutical press, London. 2003; 455.
21. Arias M J, Gines J M, Moyano J R, Perezmartinez J I, Raborsco A M; Influence of the Preparation Method of Solid Dispersions on Their Dissolution Rate - Study of Triamterene-D-Mannitol System. *Int J Pharm*. 1995; 123:25-31.
22. Ravi T K and Gandhimati M; Spectrophotometric analysis of roxithromycin in tablet formulations, The Esteran pharmacist. 2000; 21-122.
23. Bankar G S, Anderson N R, In Lachman L, Lieberman H A and Kanig JL; The Theory and Practice of Industrial Pharmacy, 3rd Ed, 4th Indian Reprint, Verghese Publishing House, Bombay. 1991; 297.
24. Pharmacopoeia of India, 2nd Ed, Controller publications, New Delhi. 1996; 740.
25. Pharmacopoeia of India, 4th Ed, Controller publications, New Delhi. 1996; A-80.
26. Pharmacopoeia of India, 4th Ed, Controller publications, New Delhi. 1996; A-82.
27. USP-24, NF-19, US Pharmacopoeial Convention Inc, Rock ville. 2000; 1941.
28. Khan K A; The concept of dissolution efficiency. *J Pharmacol*. 1975; 27:48-49.