Research Article

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DESIGN OF ORALLY DISINTEGRATING TABLET OF HYDROCHLORTHIAZIDE AND IT'S EVALUATION

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ABSTRACT
The aim of present work was to show the effect of various superdisintegrant on the disintegration time and *in vitro* drug release rate. In this study, an attempt had been made to prepare orally disintegrating tablets of the Hydrochlorthiazide using co-processed super disintegrant following direct compression method. Sodium starch glycolate, crospovidone and starch were used in different concentrations as the super disintegrant. The tablets were evaluated for diameter, thickness, hardness, friability, weight variation, wetting time, disintegration time, dispersion time, drug content and in vitro dissolution studies. Friability value of none of the formulation exceeds 0.245 %. The dispersion time of all Formulation were found to be in between 17.95(±0.06) to 55.61(±0.06) seconds. The wetting time of all the tablets was in the range 25.70 - 52.70 seconds. Overall, the formulation A5 containing 4 % w/w of co-processed superdisintegrants (1:1 mixture of crospovidone and sodium starch glycolate) was found to be promising and has shown an *in vitro* dispersion time 17.95 sec., wetting time 21.14 sec and disintegration time 17.05 sec. Percentage cumulative drug release of formulation A5 was found to be 98.51% that is maximum % drug release than other formulation. Formulation A5 containing 4%w/w of co-processed superdisintegrant (1:1 mixture of Crospovidone and sodium Starch glycolate) , using direct compression method was found to be the best formulation that has minimum disintegration time, wetting time hence this formulation was selected for In-vitro dissolution study and more than 95% drug was dissolved within 15 min.
Keywords: Orally disintegrating tablet, Hydrochlorthiazide, sodium starch glycolate, crospovidone, starch, disintegration time and co-processed superdisintegrants.

INTRODUCTION

Pharmaceutical technologists have developed a novel oral dosage form known as Orally Disintegrating Tablets (ODTs) Patients for whom chewing is difficult or painful can use these new tablets easily. ODTs can be used easily in children who have lost their primary teeth but do not have full use of their permanent teeth.[1] Recent market studies indicate that more than half of the patient population prefers ODTs to other dosage forms[2] and most consumers would ask their doctors for ODTs (70%), purchase ODTs (70%), or prefer ODTs to regular tablets or liquids (>80%)[3]. The US Food and Drug Administration Center for Drug Evaluation and Research (CDER) defines, in the 'Orange Book', an ODT as "a solid dosage form containing medicinal substances, which disintegrates rapidly, usually within a matter of seconds, when placed upon the tongue"[4].

Hydrochlorothiazide is the diuretics of the benzothiadiazine group and has proved very important in the management of mild to moderate hypertension. It inhibits sodium reabsorption in the distal tubules causing increased excretion of sodium and water as well as potassium and hydrogen ions. Hydrochlorothiazide is poorly water soluble drug having plasma half life of 6-8 hrs[5]. On the basis of these considerations, in the present study it was proposed to formulate an oral delivery device, in the form of rapidly disintegrating tablets by using direct compression technology, with the aim of reaching a high serum concentration in a short period of time. In this study, effort has been made to formulate fast disintegrating tablet of hydrochlorothiazide using two co-processed disintegrant, Crospovidone and Croscarmellose sodium. Effect of different concentration of disintegrant on disintegration time and drug release was studied.

MATERIAL AND METHODS

Hydrochlorthiazide (API), microcrystalline cellulose (diluent), starch, sodium starch glycolate, crospovidone as a disintegrant, d-mannitol (filler), aspartame (sweetening agent), magnesium stearate, talc.

Compatability study

IR spectroscopy is one of the analytical techniques useful in detecting chemical interactions. IR spectra of pure drug and in combination with polymer are shown in figure. The pure drug sample of Hydrochlorthiazide shows the characteristic peaks[6] as shown in table 1. The IR spectra of Hydrochlorthiazide with co-processed superdisintegrants (1:1) ratio are shown in figure 1 and 2. Pure drug showed characteristic absorption bands at wave numbers of 1335, 1320, 1150, 1165, 3268, 3369, 3170 1602 and 1060cm^{-1} and the formulation containing co-processed mixture showed similar characteristic absorption bands in the range without significant change in the wave number indicating no chemical interaction between drug and the polymer.

Standard calibration curve of Hydrochlorthiazide

Hydrochlorthiazide has a λmax at 272 nm in 6.8 pH buffer and obeys Beer's law in concentration range of 1-20µg/mL in phosphate buffer pH 6.8. (figure 3)

Experimental work

The actual process of developing co-processed excipients involves the following steps. The excipients for

formulation of co-processed excipients were selected by carefully studying their characteristics, incompatibilities with other excipients and also with the drug. The ratio or proportion of excipients for co-processing was selected according to their use in formulation. Crospovidone and sodium starch glycolate were used in different ratio (1:1, 1:2 and 1:3). Weigh accurately the excipients according to their ratios and mixed together in a polybag for few minutes. Then this mixture of excipients were sifted through sieve no #60 to obtain the required particle size. This mixture was added to 65 mL of isopropyl alcohol. The contents of the beaker (250 mL capacity) were stirred on a magnetic stirrer. The temperature was maintained between 65ºC and 70ºC, and stirring was continued till most of isopropyl alcohol evaporated (Solvent evaporation method). The wet coherent mass was granulated through 60-mesh sieve. The wet granules were dried in a tray dryer at 60ºC for 20 minutes. The dried granules were sifted on 60-mesh sieve and stored in airtight container till further use.

Tablet preparation by direct compression method

Fast disintegrating tablets of hydrochlorothiazide was prepared according to Table 2. All the excipients without magnesium stearate and talc were mixed uniformly followed by addition of magnesium stearate and talc. The prepared powder blend was evaluated for various parameters like bulk density, tapped density, angle of repose, compressibility index and Hausner ratio. After evaluation of powder blend, the tablets were then compressed (200 mg) on Cadmac rotary press machine, to obtain a tablet of hardness 3.65kg/cm^2.

Table 1: IR absorption of Hydrochlorthiazide

wave number cm^{-1}	Functional Groups
1335, 1320, 1180, 1150 and 1165	SO2
1603	heterocyclic ring structure
and 1058	S-N bond stretching
3268, 3369 and 3170	N-H stretching

Table 2: Formulation details of Hydrochlorthiazide tablets A1-A13

Ingredients	Category	A1	A2	A3	A4	A5	A6	A7	A8	A9	A10	A11	A12	A13
Hydrochlorthiazide	Diuretic	_	25	25	25	25	25	25	25	25	25	_	_	_
Crospovidone	superdisintegrants	**4**	**4**	2.75	2	_	_	_	8	_	_	8	_	_
sodium starch glycolate	superdisintegrants	4	4	5.25	6	_	_	_	_	8	_	_	8	_
Starch	superdisintegrants	_	_	_	_	_	_	_	_	_	8	_	_	8
co processed superdisintegrants (cp+ssg)	superdisintegrants	_	_	_	_	8	8	8	_	_	_	_	_	_
Magnesium sterate	Lubricant	2	2	2	2	2	2	2	2	2	2	2	2	2
Talc	glidant	4	4	4	4	4	4	4	4	4	4	4	4	4
Aspartame	sweetening agent	4	4	4	4	4	4	4	4	4	4	4	4	4
Menthol	flavoring agent	2	2	2	2	2	2	2	2	2	2	2	2	2
Avicel pH102	diluent	40	40	40	40	40	40	40	40	40	40	40	40	40
D-mannitol	filler	140	115	115	115	115	115	115	115	115	115	140	140	140
total weight up to		200	200	200	200	200	200	200	200	200	200	200	200	200

Table 3: Evaluation parameters of formulation A1-A13

Batch no.	Thickness in mm (± s.d.)	Friability %	Hardness kg/cm^2 (± s.d.)	Wetting time (seconds) (± s.d.)	Dispersion time (seconds) (± s.d.)	Disintegration time (seconds) (± s.d.)
A1	3.67±0.02	0.09	3.3±0.1	42.63±1.8	40.76±0.6	19.2±0.01
A2	3.68±0.003	0.1	3.5±0.005	43.25±0.5	19.09±0.04	19.20±0.3
A3	3.65±0.03	0.15	3.66±0.28	52.70±0.4	38.88±0.3	27.7±0.2
A4	3.66±0.03	0.22	3.00±0.05	52.41±0.5	42.39±0.6	30.89±0.4
A5	3.57±0.09	0.24	3.16±0.2	21.14±1	17.95±0.06	17.05±0.04
A6	3.82±0.01	0.24	3.65±0.2	25.70±1.1	28.01±0.01	21.57±0.07
A7	3.76±0.09	0.23	3.16±0.2	32.47±0.4	31.01±0.01	23.98±0.03
A8	3.79±0.08	0.18	3.48±0.04	33.84±0.5	30.43±0.26	22.26±1.06
A9	3.70±0.05	0.2	3.28±0.09	31.39±1.1	31.33±0.18	26.51±0.02
A10	3.63±0.09	0.24	3.21±0.05	26.52±0.4	39.26±0.07	28.82±0.05
A11	3.71±0.2	0.22	3.35±.008	39.23±1.3	45.65±0.06	60.11±0.01
A12	3.72±0.1	0.19	3.31±0..08	48.03±0.9	40.42±0.09	60.18±0.005
A13	3.80±0.1	0.24	3.35±0.07	50.09±0.1	55.61±0.06	120.16±0.01

Table 4: *In vitro* % cumulative drug releases and % drug content of formulation A2-A10

Formulation no.	% Drug content n= 6(± S.D.)	% cumulative drug release n= 6(± S.D.)
A2	99.423±0.271	97.12± 0.2
A3	98.961±0.219	97.01± 0.7
A4	98.846±0.271	94.83± 1.0
A5	100.15±0.369	98.51±0.8
A6	99.03±0.235	96.69±0.2
A7	98.230±0.478	96.24±0.6
A8	98.269±0.235	94.99±0.1
A9	98.153±0.21	94.93±1.0
A10	98.00±0.219	94.54±0.5

Table 5: *In vitro* dissolution parameters in phosphate buffer pH 6.8

Formulation code	Parameters						
	D_5	D_{10}	D_{15}	D_{45}	D_{60}	$t_{50\%}$	$t_{90\%}$
Conventional formulation (CF)	8.84	15.88	23.54	49.98	62.01	>15min.	>60min.
A5	64.74	87.90	95.95	97.24	98.51	3 min.	12 min.

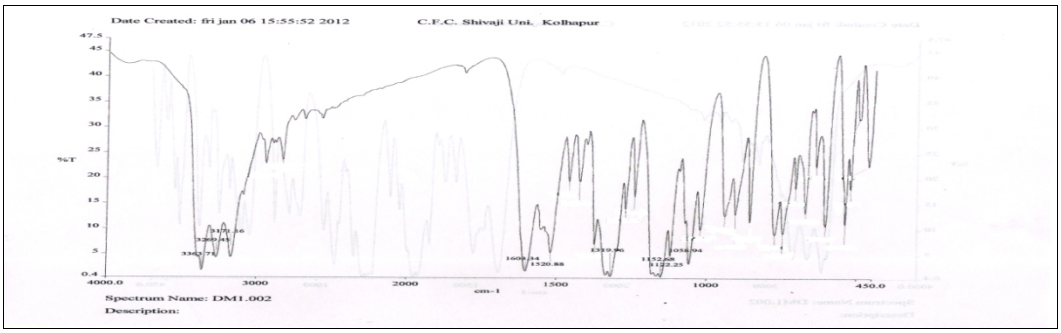

Figure 1: IR of Hydrochlorthiazide

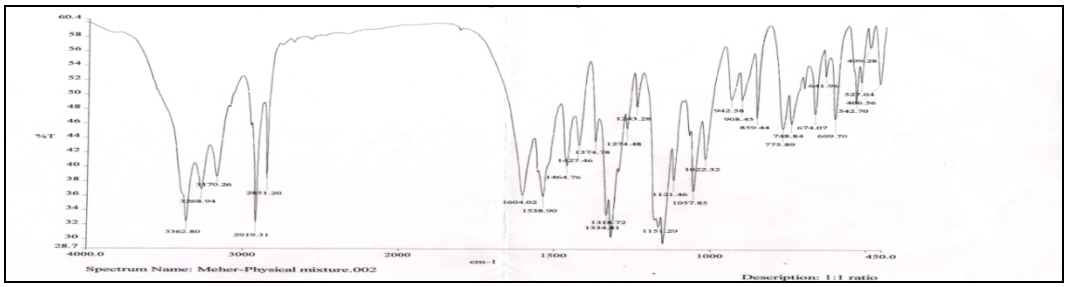

Figure 2: IR of Formulation

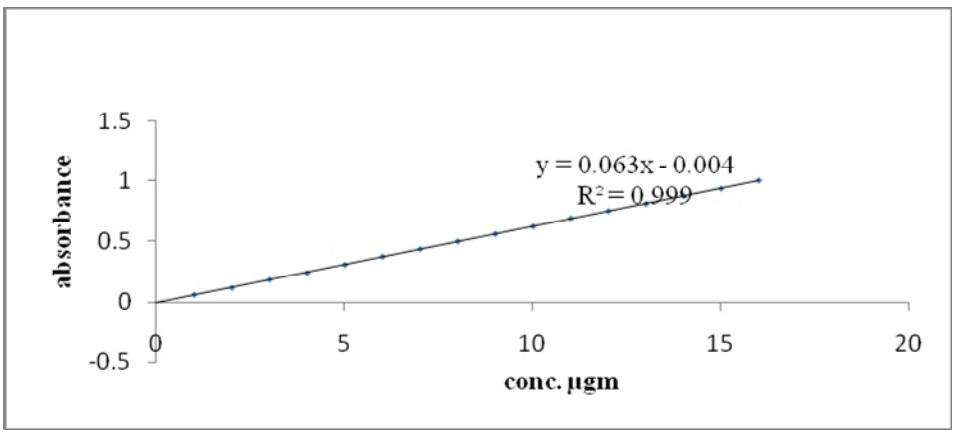

Figure 3: Standard calibration curve of Hydrochlorthiazide in pH 6.8 buffer at 272 λ max

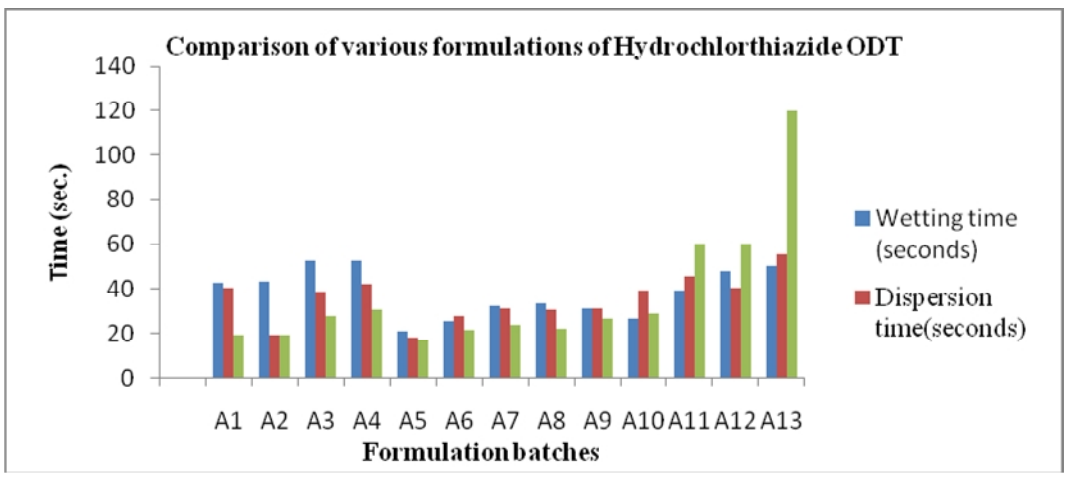

Figure 4: Comparison of various formulations of Hydrochlorthiazide ODT

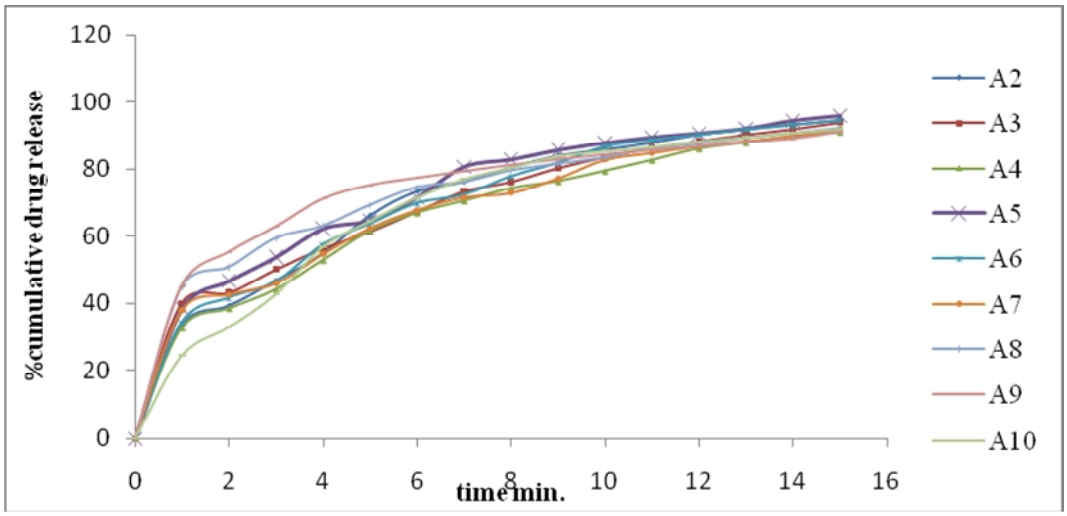

Figure 5: Comparative dissolution study of formulation A2 - A10

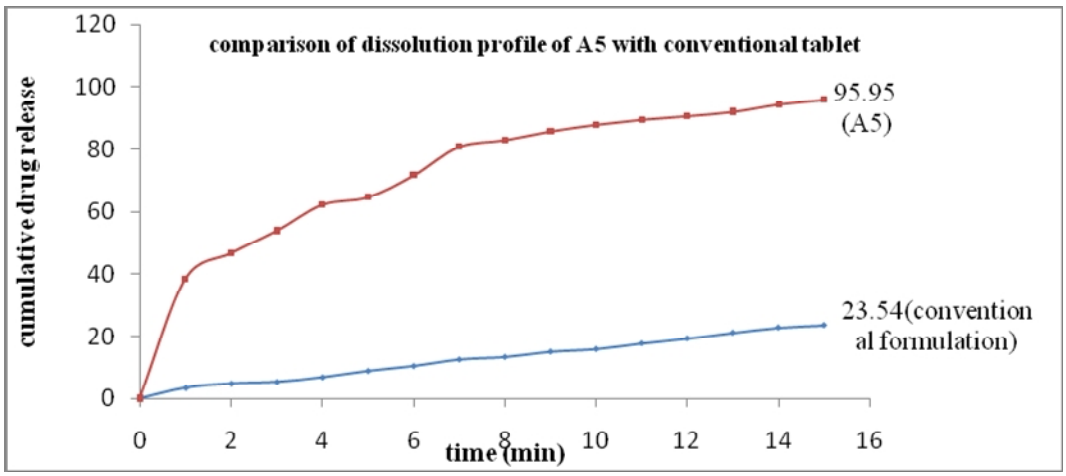

Figure 6: Comparison of dissolution profile of A5 with conventional tablet

RESULT AND DISCUSSION

Evaluation of blend properties

For each designed formulation, blend of drug and excipients was prepared and evaluated for micromeritic properties shown in Table 2. Bulk density was found to be between 0.325 gm/cm^2 to 0.587 gm/cm^2 and tapped density between 0.364 gm/cm^2 to 0.693 gm/cm^2 for all formulations. From density data % compressibility was calculated and was found to be between 13.90 % to 16.94 %. Angle of repose was found to be in the range of 27.10^0 to 32.76^0. Hausner ratio was found below 1.39. All the formulation shows the good blend of properties for direct compression and hence tablets were prepared by using direct compression technology**.**

Evaluation of fast disintegrating tablet

Weight variation test

The tablets were compressed at the specified weight (200 mg). The weights of tablet were within the ± 3% which fall within the acceptable weight variation range of ± 7.5% as per USP. Hence all formulation passed the weight variation test.

Hardness

Hardness of all formulation was in the range of 3.3 to 3.6 kgm/cm^2. The hardness of all formulation was kept constant within the above mentioned range by adjusting the compression load in order to compare the disintegration time between the formulation prepared using different co-processed excipients. (Table 4)

% Friability

Friability value of none of the formulation exceeds 0.245 %. The results of friability indicate that the tablets were mechanically stable and could handle the rigors of transportation and handling.

Thickness

Thickness of all formulation was between 3.57(±0.09) mm to 3.80(±0.1) mm indicating fairly acceptable tabletting. (Table 4)

Disintegration time

Disintegration time is very important parameter of ODT, the internal structure of tablet that is pore size distribution, water penetration into the tablet and swelling of disintegrant substance are suggested to be the mechanism of disintegrant. The Formulation No F5 gives best disintegrating time i.e. 17.05(±0.04) seconds. (Table 4)

In-vitro dispersion time

In-vitro dispersion time was measured by the time taken to undergo uniform dispersion as per the British Pharmacopoeia. The dispersion time of all Formulation were found to be in between 17.95(±0.06) to 55.61(±0.06) seconds (Table 4)

Wetting time

The wetting time of all the tablets was in the range of 25.70 - 52.70 seconds. (Table 4)

Drug content:

Percentage drug content of all formulation was found to be in between 98 (±0.219) % to 100.15 (±0.369) % that is within the acceptable limit as per IP. (Table 5)

***In vitro* dissolution study**

In vitro dissolution study of all formulation was performed. It was observed that percentage cumulative drug release of formulation A5 was 98.51% that is maximum % drug release than other formulation[7-9]. (Table 5)

From the comparative dissolution study of various formulation it was found that 95.95 percentage drug released from formulation A5 within 15 min. Hence this batch is optimized. The wetting time of this formulation was 21.14 sec. the disintegration time was17.05 sec. and dispersion time was 17.95 sec.

Comparative dissolution study of optimized formulation A5 with marketed formulation was done as shown in the figure 6. A5 is promising fast dissolving tablet formulation containing co-processed superdisintegrants in 1:1 ratio, D_5 is percent drug released in 5 min, D_{10} is percent drug release in 10 min, D_{15} is percent drug release in 15 min, D_{45} percent drug release in 45 min, $t_{50\%}$ is time for 50 % drug dissolution, $t_{90\%}$ is time for 90% drug dissolution

CONCLUSION

From the ODT tablets study, we concluded the concentration 1:1 of superdisintegrant that has minimum disintegration time, dispersion time and wetting time within the limits i.e. less than 60 sec and it was selected for drug incorporation.

From the result of the study, it was concluded that formulation A5 containing 4%w/w of co-processed superdisintegrant (1:1 mixture of Crospovidone and sodium Starch glycolate), using direct compression method was found to be the best formulation that has minimum disintegration time, wetting time hence this formulation was selected for *In-vitro* dissolution study and more than 95% drug was dissolved within 15 min.

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REFERENCES

1. Mizumoto T, Masuda Y, Takeshi Y, Estuo Y, Katsuhide T. Formulation design of a novel fast disintegrating tablet. Int J Pharm, 2005; 306(1-2): 83–90. http://dx.doi.org/10.1016/j.ijpharm.2005.09.009 PMid:16257154
2. Deepak K. Orally disintegrating tablets. Tablets and Capsules, 2004; 7: 30-35.11. Brown D. Orally disintegrating tablets: Taste over speed. Drug Deliv Tech, 2001; 3(6): 58-61.
3. Brown D. Orally disintegrating tablets: Taste over speed. Drug Deliv Tech, 2001; 3(6): 58-61.
4. US Food and Drug Administration, CDER Data Standards Manual. 2003. http://www.fda.gov/ cder/dsm/DRG/drg00201.htm. Accessed 6February 2007.
5. Satoskar RS, Bhandakar SD and Ainapure SS. Pharmacology and Pharmacotherapeutics, 17th Edition Popular Prakashan, Mumbai. 2001: 353-449.
6. United State Pharmacopoeia XXIV NF 30, 2007, United States Pharmacopoeial Convention Rockville
7. Anonymous. Indian Pharmacopiea 2007 vol.2, pp 177-182 and 662-665
8. Liberman HA, Lachman L, Schwartz JB eds. Tablet: volume I, New York N Y, Marcel Dekker Inc. 1990, pp 131-245
9. Satinder A. Impurities evaluation of Pharmaceuticals, copyright©1998 by Marcel Dekker, Inc.New York, pp 9

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